Control of Ventricular Arrhythmias by an Antilipolytic Treatment Used During Acute Myocardial Infarction In Man.

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DECLARATION

This thesis has been composed by me and the original clinical work presented was carried out by me during the tenure of a research fellowship in the Department of Cardiology in the University of Edinburgh. The electrophysiological measurements and sample collections were made by me and assistance with biochemical measurements is acknowledged in the thesis.

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ABSTRACT OF THESIS

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Title of Thesis Control of Ventricular Arrhythmias by an Antilipolytic Treatment used During Acute Myocardial Infarction in Man.

Coronary heart disease is in 1977 the leading cause of death in nearly all industrialised countries. The majority of deaths occur within 1 hour of the onset of symptoms of a heart attack and the principal cause of death is ventricular fibrillation.

The purpose of the work presented in this thesis is fourfold;

1. to review the literature on the relevance of cardiac arrhythmias to death from coronary heart disease.

2. to assess the evidence that, following acute myocardial infarction, a combination of local and systemic metabolic changes may increase the frequency of cardiac arrhythmias.

3. to propose that in man, one of these changes, a rise in plasma concentration of free fatty acids, can be reversed in the acute phase of myocardial infarction by the administration of a nicotinic acid analogue.

4. to test by a controlled clinical trial the hypothesis that (a) such administration would reliably result in a lowering of free fatty acids concentrations and (b) that this lowering of free fatty acids would result in a reduction in the incidence of ventricular arrhythmias.

The results obtained from pilot studies and a double blind trial demonstrate:-

i) that free fatty acids can be lowered safely in man with acute myocardial infarction.

ii) that where free fatty acids were successfully lowered within 5 hours of the onset of symptoms of a heart attack, there was a reduction in the incidence of ventricular arrhythmias.

This work is the only known clinical test of the hypothesis that raised plasma free fatty acids may cause ventricular arrhythmias during acute myocardial infarction in man.

CONTENTS

THESIS

The purpose of this work is fourfold.

1. to review the literature on the relevance of cardiac arrhythmias to death from coronary heart disease.

2. to assess the evidence that, following acute myocardial infarction, a combination of local and systemic metabolic changes may increase the frequency of cardiac arrhythmias.

3. to propose in man, that one of these changes, a rise in plasma concentration of free fatty acids (FFA), can be reversed in the acute phase of myocardial infarction by the administration of a nicotinic acid analogue (NAA).

4. to test by a controlled clinical trial the hypothesis that a) such administration would reliably result in a lowering of FFA concentrations and b) that this lowering of FFA would result in a reduction in the incidence of ventricular arrhythmias.

INTRODUCTION

Coronary Artery Disease

The mechanism by which disease of the coronary arteries can interrupt normal cardiac function and lead to sudden death has been studied ever since William Harvey first described the function of the coronary arteries in De Motu Cordis in 1628. ".... aut ipsius cordis caro, quae rectius per arteriam coronale nutritur." Both Morgagni in De Sedibus (1761) and Heberden in his commentaries on the history and cure of diseases (1802), related angina pectoris to sudden death, while Alan Burns and Edward Jenner related angina pectoris to pathological evidence of coronary artery disease. The earliest recorded clinical and pathological diagnosis of coronary artery occlusion as the cause of sudden death was made by Adam Hammer writing in Wiener Medicinische Wochenschrift in 1878, and technical advance allowed Pardee, in 1920, to describe changes in the electrocardiogram following coronary occlusion.

Only in the last fifteen years has there been any consistent development in the knowledge of the systemic and local metabolic responses to occlusion of the coronary arteries. The hypothesis that there may be a causal relationship between one of these metabolic abnormalities and the serious sequelae of a clinical heart attack was published as recently as 1970 (Kurien and Oliver, 1970).

The Problem of Sudden Death From Coronary Heart Disease

Coronary heart disease (CHD) is, in 1977, the leading cause of death in nearly all industrialised countries. In Britain as a whole, the reported mortality from CHD has increased steadily since 1925, and the pattern of change in Scotland since 1950 is shown in Figure 1.

Scotland has a particularly high incidence of CHD, and in 1972, a total of 1858 episodes of suspected heart attack were recorded in the city of Edinburgh alone. Of these, 999 were confirmed as myocardial infarction (Armstrong et al, 1972). Within four weeks of the onset of their symptoms of heart attack, 548 (55%) of these persons were dead. The majority died in the first 24 hours of illness, the median time of death being 1 hour 54 minutes from the reported onset of symptoms suggestive of a heart attack. 50% of the deaths occurred in the first hour of illness, and as a consequence of the abrupt onset of the illness and its short duration, 61% were medically unattended between the onset of symptoms and death. This experience has been confirmed in Ireland, Sweden and U.S.A. (McNeilly and Pemberton, 1968; Wikland, 1971; Biork and Wikland, 1972; Kuller and Fisher, 1966; Spiekerman et al, 1962) and is reviewed by Prineas and Blackburn (1975).

Despite the introduction of coronary care units more than 50% of patients dying from myocardial infarction still do so within 1 hour of the onset of their symptoms and without medical help even in the most highly organised centres. It becomes apparent, therefore, that new concepts of the management of myocardial infarction are required.

The concept that death in patients with acute heart attacks can be due to electrophysiological disorganisation as well as to the actual loss of cardiac muscle bulk has been revealed by recent experiences in static coronary care areas and mobile resuscitation units.

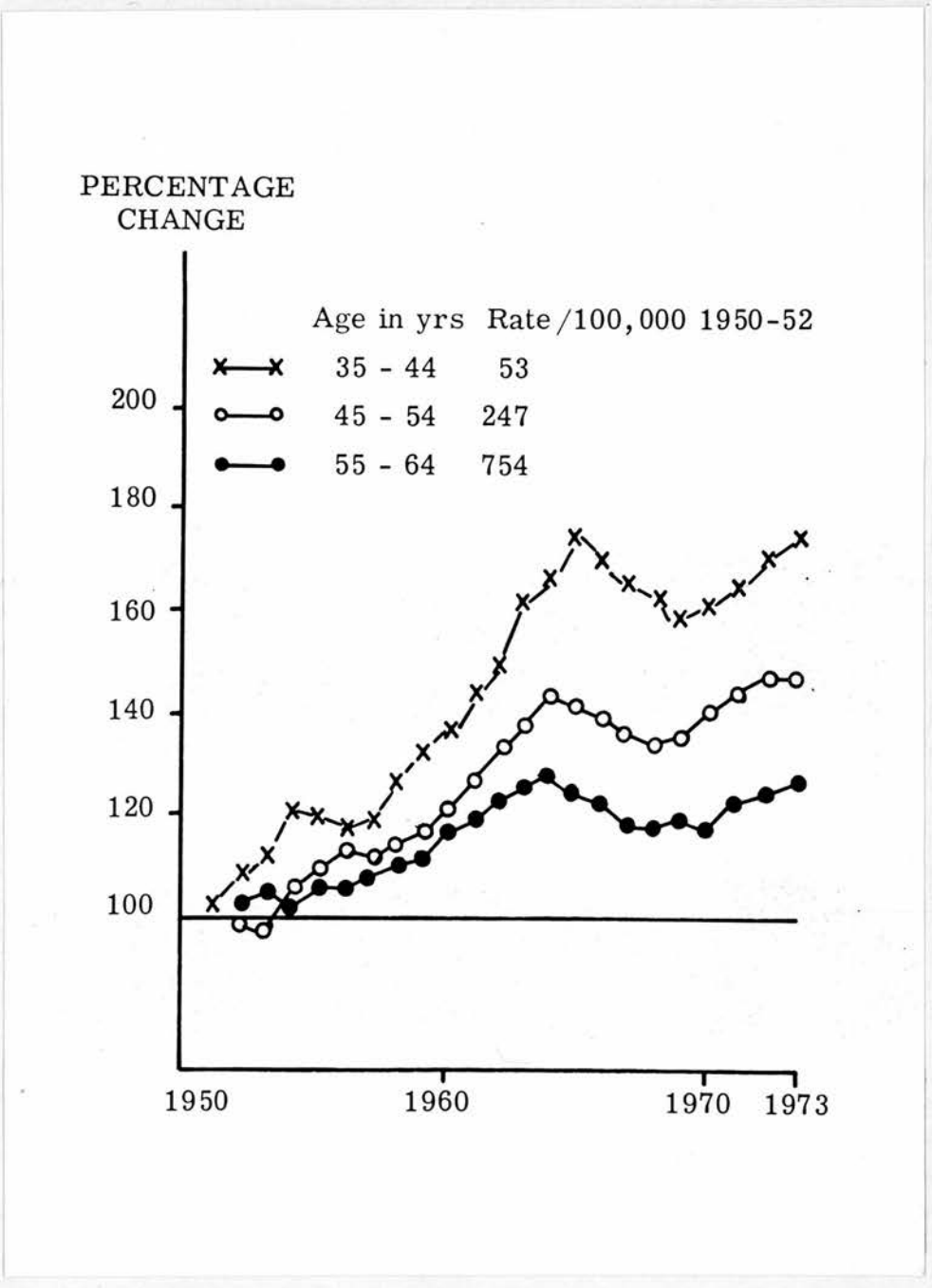

Figure 1. Percentage change in death rates from I.H.D. Scotland, 1950 - 1973. (Taken from Oliver, M.F., European Symposium on Myocardial Infarction, 1976, Turnberry).

It seems certain that early fatalities, including the majority of sudden deaths, are predominantly due to disorganised ventricular rhythms (Lawrie et al., 1967; Lown et al, 1967; Cobb et al, 1975; Julian, 1976). Although atheroma of all three main coronary arteries is found in some people dying of myocardial ischaemia, evidence of complete coronary artery occlusion, and light microscopic evidence of infarction, are often lacking in patients who die suddenly (Spiekerman et al, 1962; Adelson and Hoffman, 1961; Cobb et al, 1975). Even the newer staining techniques reveal areas of actual necrosis in no more than 50% of such patients. When these lesions are found they are often insufficient in size to compromise mechanical cardiac activity, and in patients rapidly resuscitated from cardiac arrest evidence of myocardial infarction may fail to develop. The subsequent life expectancy in these cases may not differ from that for patients with proven infarction who did not have catastrophic ventricular arrhythmias (Lawrie et al, 1967; Geddes et al, 1967; Stannard and Sloman, 1969; McNamee et al, 1970).

Cardiac arrhythmias in patients without serious infarction may thus be numerically important in the whole spectrum of death from coronary heart disease. A reduction in their frequency by therapeutic intervention might, therefore, make a valuable contribution to a lower mortality from this disease.

PART I

INTRODUCTION

Ventricular Arrhythmias in Coronary Heart Disease

Ectopic ventricular excitation is a common accompaniment of coronary heart disease in both the asymptomatic and symptomatic phases. Ectopic excitation produces extremely variable electrocardiographic patterns, and can be either single ectopic discharges from one or more foci, couplets and paroxysmal runs of ectopic beats, or ventricular fibrillation. The ectopic rythms are often paroxysmal in the individual, and not all types will necessarily occur in one individual at any stage in the disease.

The variable patterns of the ventricular arrhythmias and their paroxysmal occurrence, makes definition and quantitation of each arrhythmia difficult, and the ventricular arrhythmias described in the following review of published work, were inconsistently defined. In the interpretation of the findings in the original studies in this thesis the following conventions are used:-

Ventricular Premature Beats

Ventricular premature beats (VPB) include all isolated ventricular contractions occurring as the result of premature discharge from a focus in the ventricular wall. The only type of VPB described separately is that in which the ECG shows the initial deflection of the ectopic complex occurring before the end of the T wave of the preceding beat irrespective of whether that beat is sinus or ventricular in origin. This is described as the R upon T phenomenon (Smirk, 1949; Smirk and Palmer, 1960). Further refinements of this definition have been used by other authors, i.e. R-R interval 85% of the preceding QT interval (Lown and Klein, 1969) and R occurring within 40 ms. of the apex of the T wave (Vellani, 1972) have both been used to describe the R upon Apex T

phenomenon. In the results section of this thesis the actual number of R waves falling at any point upon a preceding T wave will be given. The definition given by Vellani will then be applied to describe any R wave falling upon the apex of a preceding T wave.

Ventricular Tachycardia

Ventricular tachycardia (VT) represents variable numbers of consecutive VPB's occurring regularly or irregularly at rates from 70-200 or more per min. Within this description many arbitrary definitions have been made and a comparative review of past studies is, therefore, difficult. In the results section of this thesis VT is defined as 4 or more consecutive VPB's occurring at an overall rate of greater than 100 per min. (The same pattern of VPB's at rates less than 100 per min. has been described as Accelerated Indioventricular Rhythm. Because this rhythm has never been considered to be associated with an excess mortality from ventricular fibrillation, it is not described in the results section of this thesis.) In addition to this arbitrary definition of VT the actual R-R intervals between the consecutive VPB's which constitute VT will be described.

Ventricular Fibrillation

Ventricular fibrillation (VF) is defined as totally disorganised electrical activity of the myocardium and classified into Primary, Complicating and Agonal as defined by Oliver et al (1967).

CHAPTER 1

Experimental Production of Ventricular Arrhythmias

Experimental work has attempted to reproduce, in animals, the various arrhythmias recorded in man, and to relate these to the occurrence of ventricular fibrillation in man. Large electrical stimuli given to the surface of the ventricles during the inscription

of the T wave (de Boer, 1920) produce a single VPB, or if the stimulus is given during the so called Vulnerable Period can produce VT or VF (Wiggers, 1940; Wiggers and Wegria, 1940; Moe, 1941). This finding prompted the hypothesis that although a single VPB in man is in itself insufficient stimulus to produce VF, multiple consecutive VPB's occurring during the vulnerable period may have a cumulative effect such that the VF threshold is lowered and a later single ectopic beat might then be able to initiate VF (Wiggers et al, 1940; Wallace, 1968).

The type of VT induced in these experiments was rapid, persistent and unifocal, and accompanied by falling blood pressure. This is to be contrasted with the type of VT most commonly seen in man with AMI which is often multifocal, usually of short duration and self terminating. The experimentally induced VT does, however, resemble the VT of the vulnerable period which begins during the inscription of the T wave as described in man with AMI (Lown, 1969; Mogensen, 1970). This is the usual commencement of VF where this has been observed in man.

There is now much evidence that those factors which increase the time taken to recover from the refractory state predispose to VF (Han and Moe, 1964; Han et al, 1966). Coronary artery ligation has been shown to increase the length of the vulnerable period but does not significantly lower the energy threshold required to produce VF. There is also evidence, in animals, that when coronary artery ligation is carried out there are apparently two common patterns of arrhythmias immediately preceding VF. Firstly a long train of VPB's may occur with the last VPB falling on or near the preceding T wave, i.e. in the vulnerable period of the preceding beat, and followed abruptly by VF. The second pattern is a single VPB triggering VT in the vulnerable period and this continues into VF.

Experimental evidence concerning the R upon T phenomenon (Fastier and Smirk, 1948) in 80 Amarin treated animals, showed that Amarin plus adrenaline always caused chaotic rhythm and that

the R upon T phenomenon occurred in many experiments before the onset of prolonged ventricular tachycardia (described as ventricular flutter).

Occasionally an ectopic R wave was seen to fall on the apex of the preceding T and then prolonged VT or ventricular flutter ensued suddenly. These changes were recorded with surface electrodes on the ventricle.

The authors of this work are careful to comment on the objections to transferring information gained from the consequences of direct heavy electrical stimulus of the animal myocardium to the clinical situation in man.

The stimuli required were large but repeated lesser stimuli did lower the VF threshold and when electrical stimulation induced VT in the vulnerable period, the VF threshold diminished to an energy level close to that expected from a single ectopic discharge in man. As a consequence, the hypothesis exists that VT of the vulnerable period or an ectopic R falling on the apex of the preceding T wave could cause VF in man with myocardial ischaemia.

SUMMARY

There is experimental evidence that direct electrical stimulation of the animal myocardium can most readily induce VF when applied during the so called vulnerable period which normally lies within $\pm$ 40 m. sec. of the apex of the T wave. Coronary artery ligation increases the length of this vulnerable period.

CHAPTER 2

The Prognostic Significance of Ventricular Arrhythmias in the Preclinical Phase of Coronary Heart Disease in Man

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The prevalence of VPB's increases with age and parallels the prevalence of Coronary Heart Disease (Hiss et al, 1960; Chiang et al, 1970). The Tecumseh study of 3,642 persons showed a higher incidence of manifest CHD in people with VPB's on a single initial ECG, and the sudden death rate in those with VPB's was three times that of the age adjusted rate in those without VPB's. The Framingham study of 2,336 persons showed similar findings with reference to the initial 12 lead ECG. A major problem in these, and in most other studies, is the length of time that the subjects could be monitored for ventricular arrhythmias consistent with screening the necessarily large populations. A standard 12 lead ECG as used in Tecumseh and Framingham has a relatively short time scale and usually reveals VPB's in approximately 8% of asymptomatic people (Lown and Wolf, 1971), but continuous monitoring for 6 hours or more always increases the yield of arrhythmias (Hinkle, 1969). In the Hinkle study, the longer period of recording thus detected more subjects with less frequent VPB's, who might be expected to have a less serious prognosis than would be associated with the presence of frequent VPB. The risk of sudden death associated with the mere presence of any VPB's was, therefore, probably initially overestimated. The risk of sudden death in patients with any VPB's seems, however, to remain independent of the other standard risk factors.

SUMMARY

Ventricular ectopic beats found on a routine ECG during population screening constitute an added risk factor for sudden

death independent of the standard risk factors for CHD. It seems likely, however, that with larger numbers of subjects and longer recordings with a consequently greater yield of VPB's, the mere presence of ventricular arrhythmias will remain a relatively poor discriminant factor in the prediction of sudden death in the individual.

CHAPTER 3

The Prognostic Significance of Ventricular Arrhythmias During Acute Myocardial Infarction

As the consequence of the extensive experimental work in animals, Smirk, in 1949, attempted to allocate prognostic significance to the R upon T type of VPB in man. From a large number of patients Smirk accummulated seventeen patients with R upon T ectopics occurring as the result of various underlying diseases of the myocardium. Six only of these were patients with myocardial infarction.

The ectopic R wave was shown falling on either the preceding sinus T wave (S/V type) or on a preceding ectopic T wave (V/V type). Examples of each type of VPB are shown in Figure 2.

A retrospective review showed that of the six cases of myocardial infarction, five had S/V ectopics of whom two died suddenly. Two patients had V/V ectopics of whom one died suddenly. Three had runs of two or more ectopics and one died suddenly. The study was interpreted as showing that the R upon T phenomenon was uncommon in AMI and that, although the evidence was insufficient, it was possible that the R upon T phenomenon had prognostic import. A follow up paper by Smirk and Palmer (1960) described a further eighty patients collected because they demonstrated the R upon T phenomenon of some form. In this group only eighteen had acute myocardial infarction. R upon T of the S/V form occurred in 82% of all eighteen ECG's, and the V/V form in only 28%. It was plain,

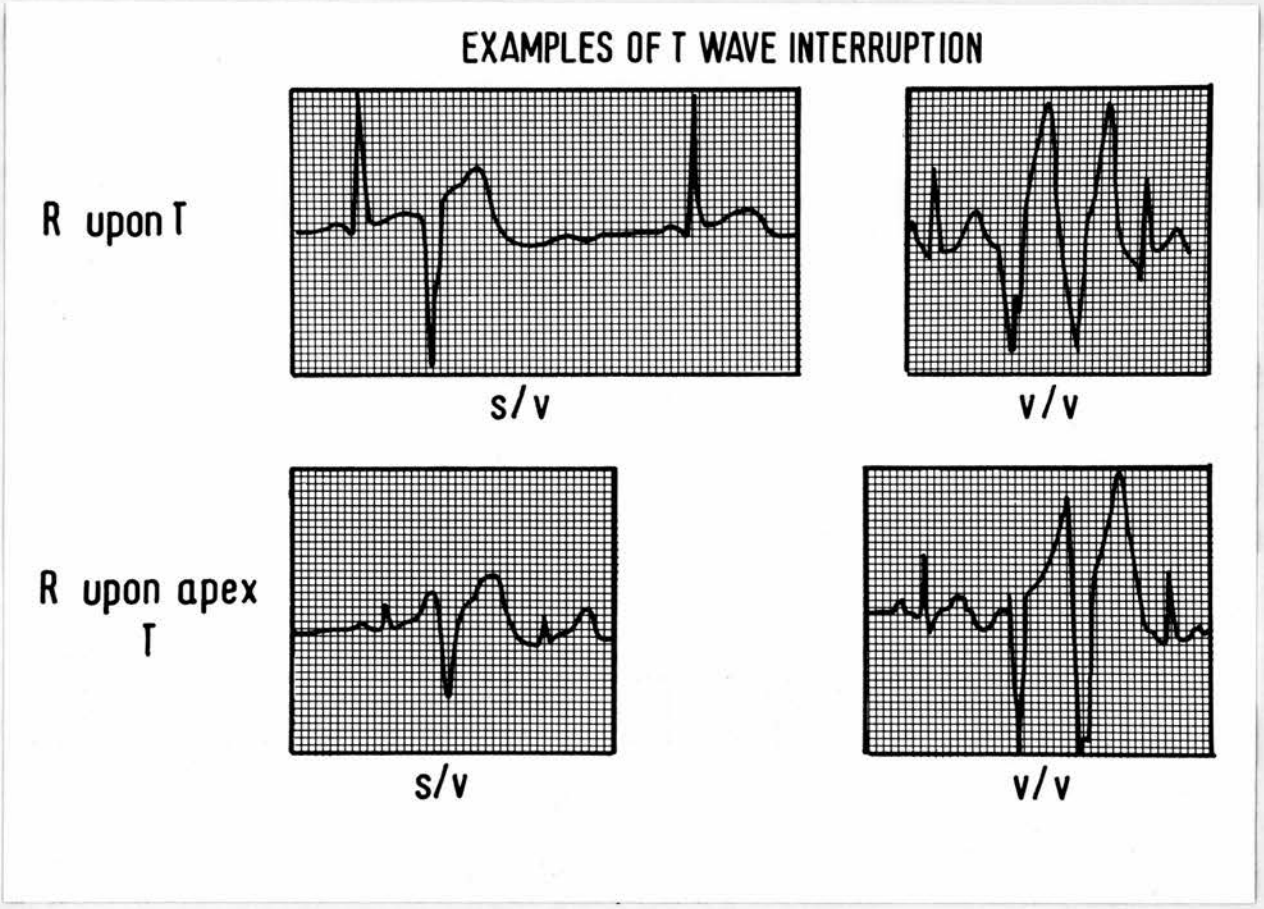

Figure 2. Examples of T wave Interruption Recorded During the work of this Thesis and Classified According to Smirk and Palmer 1960.

therefore, that the V/V form was an uncommon phenomenon on the routine ECG. Of the eighteen patients with AMI fifteen died in a mean period of 3.7 months after any R upon T was noted, and eight died suddenly. The proportions of these eight who had either S/V or V/V forms is not, however, revealed in the paper. Smirk and Palmer's interpretation of the data based on their previous experimental experience was that any form of T wave interruption by an R wave probably indicates an added danger to the patient.

Quite apart from the small numbers involved in the original studies the authors gave no comprehensive data on the risks of sudden death in patients with AMI treated in the same hospitals, and with either no evidence of arrhythmias or of arrhythmia of a different type. Relative risks cannot, therefore, be calculated.

Prospective studies of a cohort of patients whose ECG's are uniformly read can give estimates of the risk of death associated with each type of arrhythmia and an early study of this type in patients with AMI was that of Julian et al in 1964. One hundred patients with AMI were studied within 48 hours from the onset of symptoms. Thirty-one deaths occurred, twenty with preceding major ventricular arrhythmias. Ventricular Tachycardia and Ventricular Fibrillation were more common in the younger patients and during the first 24 hours of the study. The higher mortality with respect to VPB's was in the group with frequent VPB's when compared with those with infrequent VPB's. The mortality in the patients without VPB's, however, was similar to that in the patients with frequent VPB's. VF occurred in six of thirty-two patients with frequent VPB's and in seven of thirty-five without VPB's. In seven patients R upon Sinus T was seen and four of these had VF. In two of these VF occurred four and six days after the appearance of the R upon T phenomenon. Of the seven patients with R upon Sinus T, therefore, only 25% had VF in the CCU, and of the ten cases of VF seen, only four fell in the group with R upon T, and two of these would have been post CCU care by current practice. As a predictor

of VF on the standard monitoring system, the R upon Sinus T located, therefore, only two of ten patients having VF in the CCU. Five patients had R upon ectopic T of V/V form and all five survived. Ten patients were seen to have runs of between two and four consecutive VPB's and 20% of these had VF. Cases are reported by Julian et al where VF occurred despite the abolition of R upon T ectopics and VT. It was observed, however, that VT of 200/min. lasting seconds or minutes was the usual pattern of initiation of VF, and was the immediate cause of cardiac arrest.

More recently, significant suppression of R upon T and VT has been achieved with more modern drugs (Campbell et al, 1973; Talbot et al, 1973). These studies included too few patients to demonstrate whether VF was abolished, although VF only occurred on two occasions, and in the placebo group, of Campbell's study.

A similar pattern of findings to that in the earlier studies (Lawrie et al, 1968) leads to the statement that VF occurring early in the course of AMI is rarely preceded by warning arrhythmias, whereas these are commonly present in the majority of patients developing late VF. Of their cases of primary VF, 80% were in the first four hours after AMI and arrhythmic warnings rare. Of twelve cases of primary VF, only two had warning arrhythmias noted early enough to allow the institution of therapy, and in two patients on continuous taped monitoring VF developed thirty seconds after the appearance of VPB's.

A recent prospective study in 206 patients (Mogensen, 1970) using continuous slow speed paper print out of the ECG, demonstrated the R upon T phenomenon (Definition of Lown, 1969) in only ten patients, (i.e. 2% of all patients). There was only one CCU death among the patients with R upon T and five late deaths. VT occurred in 40% of all patients and 16% of patients with VT died. VT occurred most commonly in the first twelve hours and was mostly in those admitted before three hours had elapsed from the onset of symptoms. VF occurred in 6% of all patients and in 26%

of the patients with VT. Primary VF occurred in 2% of all patients but was not restricted to those with the R upon T phenomenon. A moderate association only was found between VT and R upon T, whereas a strongly significant association was present between VT and frequent and multifocal VPB's.

Retrospective analysis of the fourteen patients with VF showed that six were seen to have R upon T, and in eight the phenomenon was not observed. Of the six with R upon T two had primary VF and four had complicating VF. Of the eight without R upon T, three had primary VF and five had complicating VF. This important data, therefore, fails to demonstrate a specific relationship between R upon T and primary VF in the clinical situation of AMI in man.

Mogensen concludes that the earlier clinical and experimental evidence of R upon T initiating VF remains a strong case for treatment, but qualifies the statement by saying that the mode of onset of VF is rapid VT in most patients not on Lignocaine, often with preceding R upon T or multifocal VPB. In his later Lignocaine studies, Lignocaine was less effective against R upon T than other forms of VPB.

Similar proportions of patients having VF have been reported (Day and Averil, 1966; Adgey et al, 1971) with the higher incidences being in those groups seen earliest. A pattern of 10% of patients having VF in the first hour, 12% in the second and 2% in the third hour is the most commonly reported.

VT is detected more commonly with continuous ECG monitoring (Mogensen) and is common during periods of Sinus bradycardia. The episodes are not normally associated with a worse prognosis during AMI (Rothfeld et al, 1968; Norris and Yates, 1970).

The most recent complete analysis of a series of continuously tape-monitored patients with AMI is that of Vellani who showed that in a series of 100 patients, twenty-six had R upon T VPB's which were commonly isolated, but sometimes repetitive. S/V forms were seen in nine patients and V/V forms in twenty patients. Of the

twenty-six patients with R upon T only seven had VF. There was no obvious time relationship between VF and the R upon T events. This may be a function of the variable period of recording before VF occurred. VT tended to occur late and was seen in 70% of patients. This confirms the impression that short runs of VPB are a poor predictor of VF.

VF occurred in a total of thirteen patients, six of whom had VF without R upon T phenomenon, and only three of the thirteen had primary VF. The inter-ectopic R-R intervals preceding the VF showed a steady decrease in most cases, commonly falling by 40-60% from the first to the last interval before VF ensued. This pattern is comparable with Mogensen's finding of VT initiating VF and to Lown's VT of the vulnerable period.

The association between these arrhythmias and VF has been further questioned in two studies of 400 and 262 patients respectively where no firm relationship was found between premonitory arrhythmias and VF (Lie et al, 1974 and 1975). Unfortunately the arrhythmias were not classified in comprehensive detail and the monitoring systems have been criticized

Computor monitoring of patients with AMI (Romhilt et al, 1973; Vetter and Julian, 1975) has revealed large deficits in the detection of arrhythmias by conventional monitoring procedures. These findings must question the credibility of all previous reports, but neither of the computor studies observed sufficient patients to provide the definitive statement on the relationship between VF and the other ventricular arrhythmias.

SUMMARY

Both visual and electromagnetic taping methods of continuous ECG recording have shown that VF occurs in approximately 10% of patients reaching the CCU, and that VF is commonest in the earliest hours after AMI. Mobile CCU's confirm the distribution of

this arrhythmia and make contact with a higher number of cases. VPB and VT have been demonstrated in 70-90% of patients by continuous ECG taping and computor monitoring. This is a much higher incidence of these arrhythmias than reported from visual monitoring and they must, therefore, be relatively poor predictors of the individual who will develop VF. The R upon T phenomenon appears to be comparatively rare, occurring in approximately 2% of patients on continuous taping. Its relationship to VF is less definite on clinical grounds than previously predicted from the results of animal experiments. Nevertheless, in practice the R upon T phenomenon is still widely used as a principal indication for prophylactic antiarrhythmic therapy.

CHAPTER 4

The Prognostic Significance of Ventricular Arrhythmias in the Period After Acute Myocardial Infarction

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Pel and Dolonso (1964) studied the death rate in 1,180 men with AMI who had had a routine ECG at any time before the attack. They showed that during the attack and in the subsequent thirty days there was a higher death rate in those with any ventricular arrhythmia before the attack. Tabatznik et al (1972) reporting the continuous ECG tapes of 160 men who had survived one or more AMI over three years, showed higher death rates in men with greater than 10 VPB's per hour, multiform VPB's and VT. These findings were independent of the other standard risk factors for CHD.

The Coronary Drug Project (1973) showed that 11.5% of 2,035 men surviving AMI had one or more VPB's in a single ECG. In a three year follow up 21.7% of patients with VPB died and 11.4% of those without VPB died. Excess long term risk was associated with multiple VPB's and VT, but R upon T VPB although showing the

same trend did not demonstrate a prognostic significance for death. Kotler (1971) confirmed these findings in a further 160 men. Lown states that the mere presence of VPB's has little prognostic implication as 62% of patients with known CHD monitored for twelve hours have VPB's and, therefore, it is unlikely that they can be a powerful discriminant for death of the individual. Contrary to this view is the report that it is possible to demonstrate on an ECG of one hour's duration, a three-fold risk of sudden death in men with complex VPB's (Ruberman et al, 1977). This recent study attempts some subdivision of VPB's and although not using the classification of Smirk, unlike Lown's study it does separate R upon T events from other complex arrhythmias. At sequential points in time in the follow up period, men with R upon T or runs of VPB were at higher risk of sudden death than those with bigeminy or simpler forms of VPB.

SUMMARY

Ventricular arrhythmias after AMI identify a group with an independent risk of sudden death greater than that attributable to the standard risk factors. With continuous records these arrhythmias are detected more frequently but whilst identifying an at risk group it remains uncertain if they can identify the individual who will die suddenly of VF at any time after initial recovery from acute myocardial infarction. The importance of specific complex arrhythmias such as R upon T VPB is uncertain, probably as a consequence of their comparative rarity and poor detection by conventional survey methods. Nevertheless, continuous recordings do confirm that the detection of any complex arrhythmia may be helpful in locating at risk patients.

CONCLUSION TO PART 1

The evidence that any one ventricular arrhythmia, and in

particular the R upon T phenomenon, is causally related to ventricular fibrillation in man has been reviewed and is inconclusive.

Approximately equal numbers of people with the R upon T phenomenon have VF or escape without VF, and as many people as have VF and R upon T, have VF without preceding R upon T. A considerable number have VF without any of the forms of so called premonitory arrhythmia, particularly in the earliest phases of AMI. the abolition of VPB's, R upon T forms of VPB, and VT, does not remove the risk of developing VF although of course the quality of the therapy given may have influenced the results reported.

It might be postulated that VPB's singly or consecutively may be the harbingers of sudden death in the presence of myocardial ischaemia, if each pattern of ventricular arrhythmia represents a different stage of progression through a series of metabolic abnormalities at myocardial cell level; the decisive factor for the development of VF not being inherent in the VPB's themselves, but in the extent of metabolic disturbance which has allowed the appearance of each type of arrhythmia.

The rate at which myocardial metabolic inhomogeneity develops during ischaemic episodes may vary with the individual, and depend upon the extent of the disease of the arterial tree and the state of development of the collateral circulation. For example, a person with triple vessel disease and a sedentary mode of life might, during an acute ischaemic attack, develop local areas of metabolic imbalance, because of the lack of the facility to clear rapidly abnormal accumulations of metabolites. This would lead to early inhomogeneity of fibre activity and substantially increase the risk of VF. In other individuals a slower development of these changes would occur because of at least temporary local compensation achieved by opening of collaterals. A stepwise deterioration would then occur as the thrombotic process spread and ultimately exceeded the capacity of the compensatory mechanism. VF would then ensue. Each step in the metabolic deterioration in a given area

would allow of a different pattern of disorganised impulse formation and conduction, and, therefore, each successive arrhythmia would effectively give warning that the metabolic situation at myocardial level was deteriorating, and that the conditions allowing VF to occur, by whatever mechanism, were imminent. This progressive pattern is seen in occlusion of the coronary arteries in normal dogs and may represent the situation in some of the patients surviving to reach the CCU. This would give the impression in the CCU situation that these "premonitory" arrhythmias were in fact causally related to VF. The prognostic grading of the arrhythmias (Moss et al, 1975) could, therefore, be interpreted as an indirect grading of the degree of metabolic disturbance at myocardial level, in patients who were to some extent able to compensate at the time of acute ischaemia and, therefore, did not die suddenly of VF. Each more severe step in metabolic disorganisation would be less likely to resolve spontaneously and, therefore, in each successive group of patients a greater proportion would proceed to VF and death. This would account for the observed findings that although on experimental grounds the R upon T phenomenon has been suggested as the cause of VF, not all patients having R upon T events develop VF. The R upon T phenomenon could, however, still be the most sensitive indicator of impending death if, as Vellani suggests, it represents severe metabolic disorganisation to the extent of potassium leakage into the channels surrounding the cells. This would not then attribute the cause of VF to the R upon T phenomenon, but rather that the phenomenon represents the beginning of the last stage in deterioration before the conditions occur which favour the development of VF.

The exploration of the local metabolic changes and the concurrent systemic manifestations of AMI assume new importance as the mere removal of the ventricular arrhythmia, by suppression of myocardial cellular activity, is manifestly inadequate as a therapeutic measure, and does not necessarily prevent the progression of the

underlying metabolic changes. Intervention in these cases could, however, halt their progression and so provide a means of preventing each successive type of arrhythmia and, therefore, ultimately prevent ventricular fibrillation.

oOo

PART II

INTRODUCTION

The vulnerability of the myocardium to the development of sudden failure of normal rhythm and contraction, must ultimately depend on the extent of alteration in the normal pattern of cell metabolism caused by reduced coronary artery blood flow. These metabolic changes may be precipitated for the first time by acute massive coronary artery occlusion, or may result from minor reductions in blood flow in the circumstances of dangerous pre-conditioning of the myocardium from repeated earlier minor episodes of ischaemia. As already indicated in this thesis, the immediate consequences of any one episode of myocardial ischaemia do not necessarily progress to irreversible cell destruction even if they do reach the stage of initiating ventricular fibrillation.

The information about normal myocardial metabolic pathways has been obtained by study of animal preparations and of isolated perfused animal hearts. These findings can only be confirmed indirectly in man by derived measurements of coronary blood flow and the comparison of arterial and coronary sinus concentrations of metabolites. The use of exercise, fasting, alteration in diet and the infusion of safe amounts of test substances, e.g. catecholamines can give further indirect information about the response of the myocardial cell to these types of stresses in man. Information about the effect of acute ischaemia on the myocardium is restricted to that from experimental coronary artery occlusion in intact animals and from ischaemic perfused heart preparations. In man, with acute myocardial ischaemia or infarction the information about the metabolic changes has been restricted to studies of the systemic response to myocardial ischaemia, coronary sinus catheterisation studies, and comparison of the findings with the changes known to occur at myocardial level in animal experiments.

The comparability of the response of the human myocardium and that of animals to reduced coronary blood flow is obviously questionable, particularly in that clinical myocardial ischaemia in man is the culmination of a slowly progressive reduction in blood supply terminated by the acute event, whereas in animal experiments, relatively sudden reduction of blood flow is achieved in the previously normal heart.

The elaboration of the thesis, that intervention in the systemic metabolic abnormality following AMI in man may be reflected in metabolic changes at myocardial level which will reduce the incidence of ventricular arrhythmias, requires, therefore, an assessment of the current knowledge of the normal metabolism of the myocardium and the effect of ischaemia, as judged from experimental evaluations in animals. This must be compared with the clinical evidence in man linking the systemic metabolic response to myocardial ischaemia with the incidence of ventricular arrhythmias.

CHAPTER 1

The Metabolism of the Normal Myocardium

The normal myocardium is highly dependent upon oxidative metabolism of substrates for its supply of energy. During normal coronary blood flow approximately 75% of coronary artery oxygen is extracted during the passage of blood through the myocardium (Scheuer, 1967) and, therefore, only a limited additional amount can be extracted under abnormal conditions. The most important substrates normally used by the myocardium for the generation of energy for contraction and the maintainance of cell membrane functional integrity, are glucose, FFA, and lactate. To a lesser extent pyruvate, acetate, ketones and amino acids can be used (Olson and Piatneck, 1959). A schematic representation of energy pathways in the normal myocardium is shown in Figure 3.

Plasma FFA are generally believed to be the major source of FFA for myocardial metabolism (Bing, 1965) and their relative contribution probably accounts overall for 30-40% of total substrate utilisation. They may account for a much greater proportion in severe fasting states, and the fractional contribution of FFA thus varies with the state of fasting and exercise. The concept of substrate competition for oxidation and its effect on the contribution of FFA is reviewed by Opie (1969). He concludes that carbohydrate may become the major fuel during significant parts of the 24 hour cycle, especially during periods of prolonged exercise.

Under physiological conditions FFA are extracted by the myocardium in preference to carbohydrates (Ship et al, 1961) and a positive correlation has been demonstrated between the arterial concentration of FFA and myocardial extraction or uptake of FFA (Scott et al, 1962). It is suggested that FFA are not subject to active transmembrane transport and that their uptake is a non-energy requiring process. It may, however, be influenced, at least in

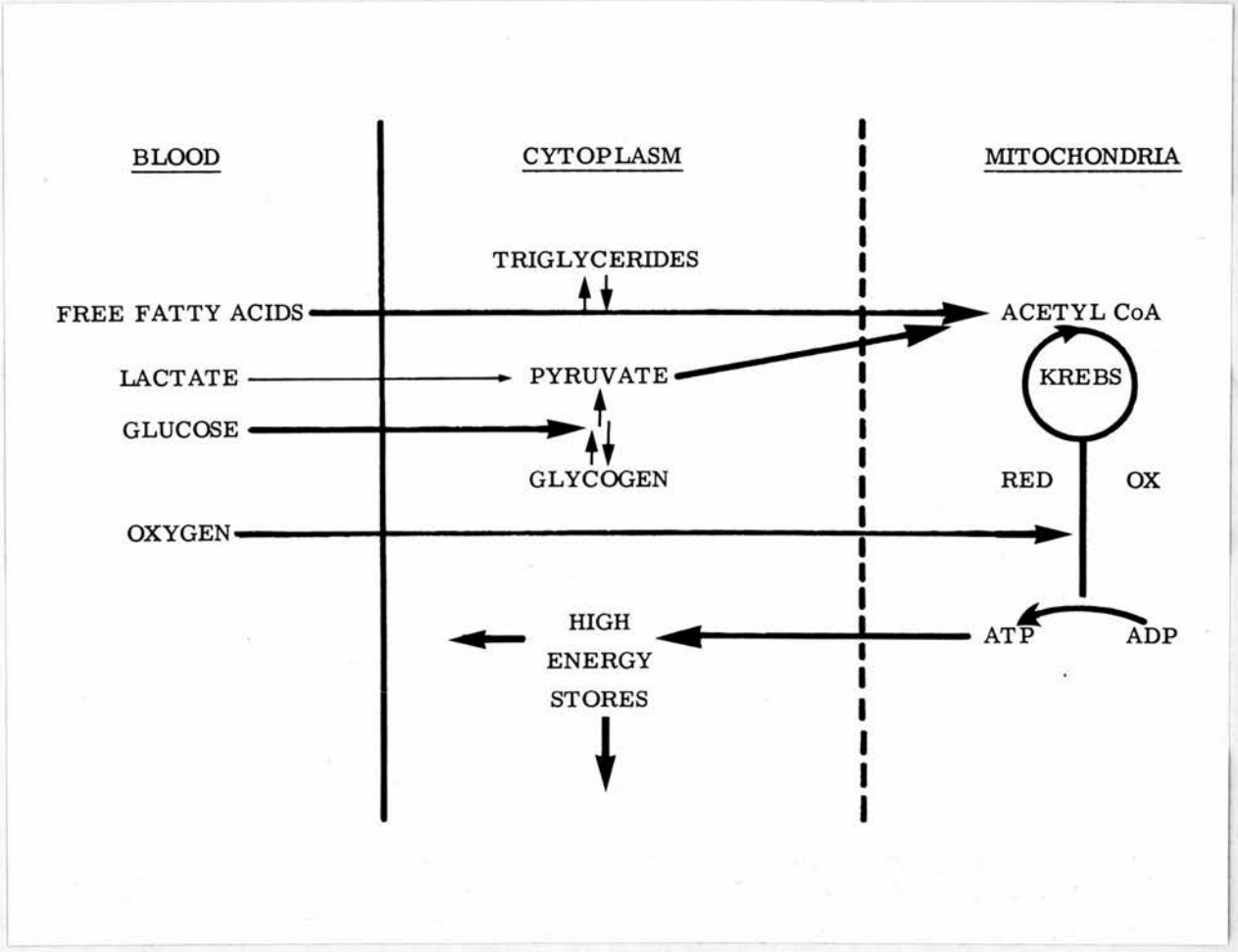


Figure 3. Energy Pathways in The Normal Myocardium.

experimental conditions, by the albumin:FFA ratio and by the degree of unsaturation of the FFA (Evans, 1964). When FFA in excess of requirements is taken up, it is stored as triglyceride and phospholipid, and during extremes of exercise and fasting, oxidisable FFA may be released from triglyceride by the action of myocardial lipase.

Glucose uptake is an active, energy requiring process and therefore is limited by the availability of its carrier (Morgan et al, 1961). Insulin accelerates membrane transport of glucose, and thus in the presence of adequate insulin the rate limiting step for the uptake of glucose becomes the rate of intracellular phosphorylation. In addition there is a threshold level below which glucose cannot be taken up, although its mechanism is uncertain. When excess glucose is taken up it is stored as glycogen which can be utilised as a source of energy in extreme circumstances. The operation of an FFA/glucose cycle has been proposed as an explanation of the control of glucose uptake and it has recently been shown that decreased plasma FFA after nicotinic acid administration is associated with increased glucose uptake (Balasse and Neef, 1973) and that increased FFA after high fat feeding is associated with a decreased glucose uptake.

Intracellular transport of substrates is necessary for their entry into the energy trapping cycle located in the mitochondria, and thereafter the main substrate catabolic pathways of glycolysis, beta-oxidation and 2 carbon degradation with the generation of high energy phosphate compounds do not differ materially from those of other tissues. The major dependence in normal circumstances on an aerobic pattern is borne out by the low content of anaerobic enzymes and high concentrations of cytochromes, with the oxidation of ADP-ATP as the final step in the energy formation in the myocardium.

The maintainance of the transmembrane electrical potentials, ultimately responsible for the electrical activity of the heart,

depends in part upon the maintainance of transcellular ionic gradients (Hodgkin and Horowicz, 1959). The Na^+ and K^+ pumping mechanisms are linked to specific ATPase systems which depend in turn on ATP for energy. This system in the heart appears to be located in the sarcotubular system (Krespi et al, 1964). If ATP supplies are jeopardised then both the electrical and contractile activities are compromised.

SUMMARY

In the normal heart the metabolic pathways form a well integrated system which is controlled by the relative quantities of high energy compounds and by their breakdown products. It is also influenced by the provision of oxygen and a balanced supply of essential substrates for aerobic breakdown. The most important substrates are FFA and glucose which are taken up by differing mechanisms. Each may assume relative importance under differing normal conditions although overall, FFA seems to be the major fuel. A complex cyclical mechanism may exist between FFA and glucose which determines the relative contribution of each at any given time of day taking into account conditions of fasting and exercise.

CHAPTER 2

The Metabolism of the Ischaemic Myocardium

In the minutes immediately following experimental coronary artery occlusion in dogs, a wide area of cyanosis appears on the epicardium and there is early loss of contractility of myocardial cells. This initial area of involvement may be much larger than the final infarcted area. These changes can occur before ECG changes and arrhythmias appear. The reduction in coronary artery blood flow results in the maximal extraction of available oxygen

but the increase obtained is limited, and is inadequate to support the normal electron transport chain and there is a consequent fall in the production of ATP. The myocardium must, therefore, resort in part to anaerobic energy production with the utilisation of differing proportions of both the usual and alternative substrates (Opie, 1971).

Glucose consumption increases at the expense of glycogen storage and the phosphofructokinase reaction is accelerated by oxygen deprivation (Scheuer, 1967; Owen et al, 1969). This speeds glycolysis which is also stimulated by ATP breakdown products and catecholamines. There is a consequent increase in pyruvate production and in the face of decreased pyruvate utilisation, pyruvate accumulates and pushes the Lactate-Pyruvate reaction towards Lactate, an increase in which is probably the one easily measured myocardial metabolic response to hypoxia (Scheuer, 1967; Gorlin, 1969). Even this does not, however, directly reflect a uniform intracellular change throughout the cyanotic area as inhomogeneity of myocardial blood flow will affect overall measurements of lactate output.

Anaerobic glycogenolysis is an apparently transient source of energy in intensely anoxic areas only in the earliest phases of ischaemia, but it ceases before the complete exhaustion of glycogen stores (Opie, 1968).

The accumulation of lipid droplets in the animal myocardium occurs within 2-6 hours of breathing an hypoxic atmosphere (Wartman et al, 1956). This occurs only in living cells and not in rapidly dying cells. The findings are confirmed in man (Scott, 1961) by study of the myocardium of children dying hypoxic deaths. Uptake and storage of FFA take place under hypoxic conditions as long as there is sufficient glucose present to support an actively glycolysing system, and as FFA uptake is non-energy requiring it continues despite a diminishing supply of ATP. An adequate supply of glucose has been shown to enhance FFA incorporation into

myocardial neutral lipid and suppress oxidation of FFA. Alpha-glycerophosphate is an important precursor of triglyceride and its availability affects the extent of FFA esterification. It is an intermediary product of glycolysis and when present in increasing concentrations stimulates FFA esterification as in conditions of partial anaerobic metabolism. During all but severely ischaemic conditions, i.e. in hypoxic but living cells, anaerobic glycolysis may produce enough ATP for intracellular transport of FFA and enough glycerophosphate for its esterification.

In the presence of high plasma FFA concentrations, therefore, uptake and storage of FFA will result in the appearance of neutral lipid droplets in the perimitochondrial zones of the cells (Brachfeld, 1969). Complete anoxia with mitochondrial death is the only situation to completely arrest FFA uptake. Where in addition FFA utilisation is restricted by oxygen lack which prevents entry into the Krebs cycle, the overall outcome might be of patchy FFA accumulation in the myocardium during episodes of ischaemia. A schematic representation of the energy pathways in the ischaemic myocardium is shown in Figure 4.

During periods of diminished ATP production the maintenance of the cell membrane ionic pumps is threatened. Under conditions of total anoxia ATP disappears from the cell in 15 minutes. At this stage the ECG begins to show an injury potential due to membrane malfunction consequent upon potassium leaking from cells. This alters the extracellular concentration of the ion and thus modifies membrane depolarisation. In ischaemic dog papillary muscle 10% of cellular potassium is lost in the first $1\frac{1}{2}$ hours of ischaemia and depletion to about 20% occurs by 24 hours (Jennings et al, 1969). Efflux of potassium from dog heart in vivo after coronary artery occlusion has also been demonstrated. This potassium loss from the ischaemic cell has been linked to the occurrence of arrhythmias although the maximal efflux of potassium into the coronary venous effluent was not related temporally to the onset of arrhythmias

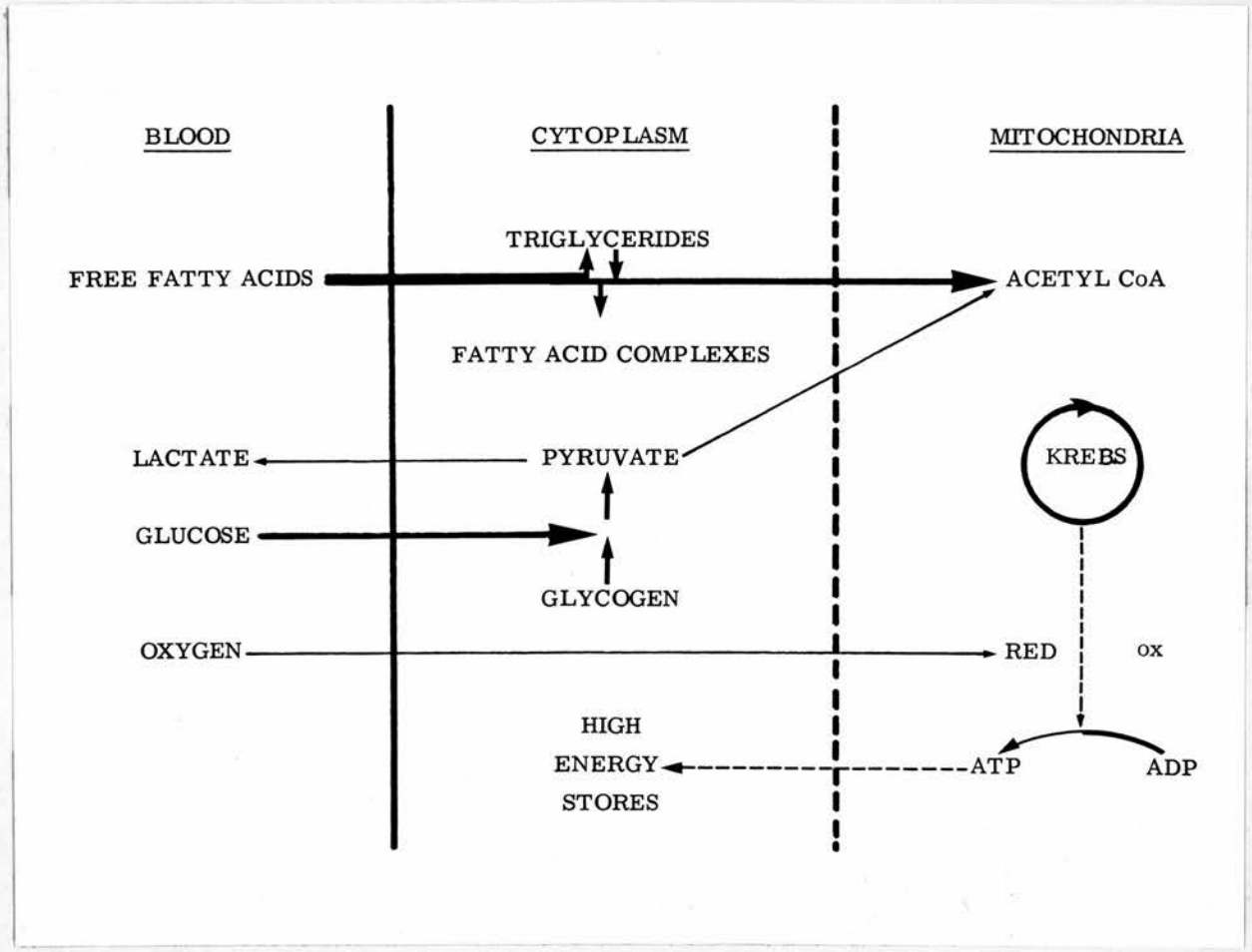


Figure 4. Energy Pathways in the Ischaemic Myocardium.

(Cherry and Myers, 1971). Injection of potassium into patent coronary arteries, with consequent high extracellular levels, has been shown to induce ventricular arrhythmias (Harris et al, 1958). The leakage of potassium from the cells and its accumulation in the continuous sheath around the conducting system would expose the cells to very high extracellular concentrations which could affect the conduction velocity and so allow the propagation of ventricular arrhythmias.

Extracellular concentrations of other electrolytes such as calcium and magnesium may also be abnormal. Surowicz discusses the relationship between relative concentrations of potassium and calcium and shows that in experimental conditions an imbalance between potassium and calcium concentrations is more closely related to severe electrical disturbance than simple potassium loss from the cell (Surowicz, 1971). The calcium ion is a major factor along with ATP in the interaction of actin and myosin on which normal contraction is based. The loss of ATP and calcium under ischaemic conditions may thus contribute to sudden failure of normal myocardial function. Low concentrations of the magnesium ion have been associated with sudden death and arrhythmias (Chipperfield and Chipperfield, 1973), and either acute depletion or a critical alteration in extracellular concentrations during acute ischaemia following upon chronic depletion, may contribute to the ionic imbalance which interrupts normal membrane function.

SUMMARY

Under ischaemic conditions the myocardium is obliged to resort to an increasing extent to anaerobic metabolism. Glucose consumption is increased at the expense of storage, and lipid accumulation occurs. This latter effect is accentuated by the reduction in FFA utilisation as FFA cannot be metabolised anaerobically and it requires slightly more oxygen for aerobic

metabolism. Furthermore, FFA inhibits glucose uptake. Consequent ATP lack threatens membrane ionic pumps and K^+ leakage occurs along with changes in relative concentrations of calcium and magnesium. The combined effects are a deterioration in membrane electrical stability and hence of conducting and contractile functions.

CHAPTER 3

The Systemic Response to Acute Myocardial Infarction in Man

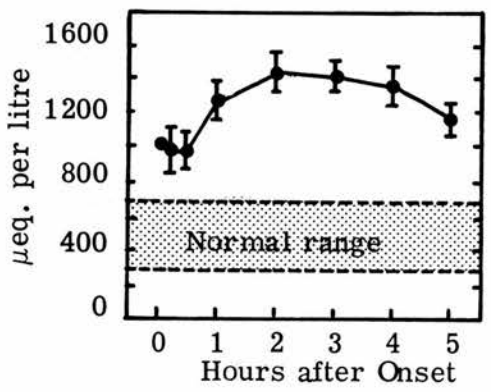
The clinical syndrome associated with acute myocardial infarction in man is accompanied by the early onset of systemic metabolic changes which result from the acute physical stress situation that has been induced. Their importance lies in their effects on the balance of the essential substrates available for support of the remaining partly ischaemic myocardium. This may be of critical importance to those areas of myocardium which are not uniformly ischaemic and contain potentially viable cells. In these regions, metabolic inhomogeneity and failing energy supply may lead to membrane instability or ultimate necrosis of the whole area.

The changes in plasma metabolites and hormones are shown in Figure 5.

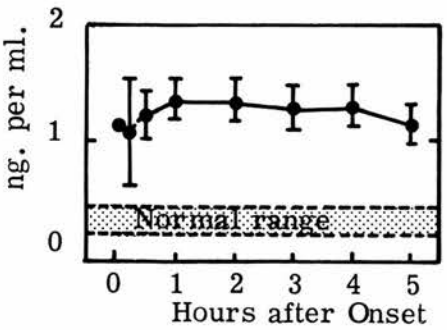
Plasma total catecholamines rise sharply within 30 minutes and remain consistently elevated at almost three times the normal level for at least 48 hours from the onset of symptoms (Vetter et al, 1974; Videbaek et al, 1972). Initially the major component is probably noradrenaline (Jewitt et al, 1969; McDonald et al, 1969) followed by an adrenaline response (Gazes et al, 1959) reflected in high urinary adrenaline during the 24 hours after the onset (Valori et al, 1967). The consequent marked catecholamine mediated β-receptor stimulation accounts for the sudden elevation in circulating FFA (Pinter et al, 1967; Carlson, 1968) which are released by adipose tissue lipolysis. Plasma FFA concentrations are in excess of

1000 μEq/L at half an hour after the onset of symptoms and reach a peak in the region of 1200 μEq/L two hours later. A fall towards normal levels commences within the first twelve hours and the normal range is regained by 24 hours in most instances. The rise is attributed to increased output from adipose tissue rather than reduction in tissue uptake (Carlson, 1968; Gupta et al, 1969), although this may be altered in patients with shock and poor tissue perfusion. Increased adipose tissue lipolysis also results in increased circulating glycerol concentrations (Carlstrom and Christensen, 1971). Another possible stimulus to lipolysis is the increased cortisol secretion in response to increased ACTH output (Nitter-Hague et al, 1972; Vetter et al, 1974). Glucose utilisation is impaired and poor insulin secretion has been reported in severely ill patients (Taylor et al, 1969). In the earliest phase plasma immunoreactive insulin is in the low normal range and in some cases may be subnormal.

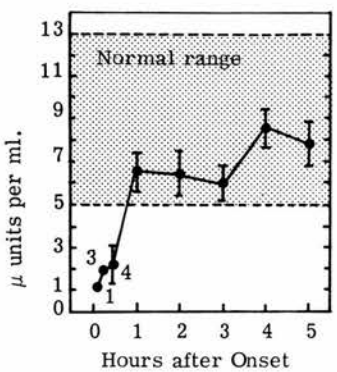
Hypoxia alone may initiate these processes but does not per se inevitably cause arrhythmias (Harris, 1966) and thus additional adverse conditions must exist before ectopic excitation can occur. Preconditioning of the myocardium may exist with lipid accumulation, but increased local and systemic catecholamine activity (Maling and Moran, 1957; Ceremuzynski et al, 1969), and K^+ leakage from the cells (Cherbakoff et al, 1957; Regan et al, 1967) are some of the acute factors. Increased concentrations of circulating unbound FFA may also have an effect by producing an increased local concentration which may then have a detergent activity on the cell membranes (Kurien and Oliver, 1970) or inhibit ATP transport across the mitochondrial membrane (Shug and Shrago, 1973).



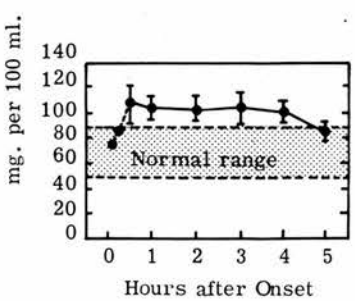
PLASMA FREE FATTY ACIDS



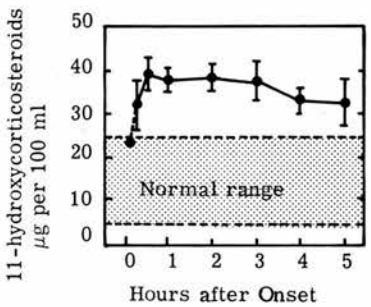
PLASMA TOTAL CATECHOLAMINES



PLASMA INSULIN



BLOOD SUGAR



PLASMA CORTISOL

Figure 5. Changes in mean concentration ($\pm$ S.E.M.) of plasma metabolites and hormones in sixteen patients with AMI (Adapted from Vetter, et al 1974).

SUMMARY

Of these systemic metabolic abnormalities occurring as a result of coronary artery occlusion, no single change so far observed can account for the development of ventricular arrhythmias or has been solely related to death in the acute episode. It seems probable, however, that very early therapeutic intervention would be required to reverse any of these changes in order to support endangered areas of myocardium sufficient to influence the clinical outcome of the event.

CHAPTER 4

The Experimental Evidence that Raised Plasma FFA Concentrations Can Have Deleterious Effects on the Ischaemic Myocardium

In experimental circumstances FFA have been shown to increase myocardial oxygen consumption (Mjøs, 1971), decrease contractility (Henderson et al, 1970), alter electrical conduction (Connor et al, 1963), increase infarct size (Kjekshus and Mjøs, 1973; Sobel et al, 1973) and possibly cause overt ventricular arrhythmias (Kurien et al, 1971; Oliver et al, 1972). In aerobically perfused, contracting, isolated rat hearts, myocardial oxygen consumption (MVO_2) can be altered by varying the supply of substrates to the myocardium (Challoner and Steinberg, 1966). Specific free fatty acids increase the MVO_2 of the potassium arrested heart and the effects of adrenaline on this preparation include an increase in the intracellular FFA concentration. This evidence has been confirmed in the normal contracting dog heart under controlled haemodynamic conditions (Mjøs, 1971). Infusion of intralipid and heparin produced plasma FFA levels up to 3000 μEq/L which in the presence of unchanged mechanical performance increased MVO_2 by about 20%. This was largely attributed to an increase in metabolic rate stimulated by high FFA concentrations.

The infusion of high concentrations of FFA into dogs produces massive platelet thrombosis and death (Connor et al, 1963) but where the thrombosis is prevented by the administration of heparin,

FFA still depresses myocardial contractility to the point of death. FFA administered to rabbits (Severeid et al, 1969) decreased coronary blood flow and the amplitude of contraction but the effect was modified by incubation of the FFA with albumin. This suggests that unbound FFA are particularly toxic to the myocardium. In experiments in the isovolumically contracting heart (Henderson et al, 1970), high FFA decreased contractility, increased the end-diastolic pressure and increased oxygen utilisation for a given tension development. This was accompanied by a decrease in MVO_2 which is contrary to previous findings and is explained on the grounds that the hearts may have been oxygen limited. The depressant effect of FFA in these experiments was increased by increasing the FFA/albumin ratio and a maximum effect was obtained at a ratio of 6:1. It has been further demonstrated in rat papillary muscle that increasing hypoxia reduces the need for increasing FFA/albumin ratio to produce myocardial depression, but that increased ratios prolong the period needed for recovery on re-oxygenation of the preparation (Henderson et al, 1970). There is also a relationship between epicardial ST elevation and free fatty acid/albumin ratios during coronary occlusion in dogs (Miller et al, 1976). In intact dog hearts the mechanical performance can be modified by FFA in ischaemic states (Kjekshus and Mjøs, 1972). The raising of FFA can cause ventricular decompensation which is reversed by the infusion of glucose and insulin with consequent lowering of FFA. Agents which increase myocardial oxygen demand have been shown to increase the size of the experimental myocardial infarction (Maroko et al, 1971). By inference, therefore, it might be expected that increased FFA concentrations, by increasing O_2 consumption, might increase the size of an infarction. This is supported by evidence that where FFA are lowered by β-pyridyl-carbinol (converted to Nicotinic Acid in the liver)(Kjekshus and Mjøs, 1973) in experimental infarction, the sum of the ST elevations over the surface of the myocardium is reduced. The increasing sum of ST

elevation and the rising FFA produced by the infusion of Isoproterenol, is also controlled by nicotinic acid. A similar effect has been observed with noradrenaline and nicotinic acid and further, that Ronicol used to inhibit an Isoproterenol induced elevation of FFA, also reduced the ST elevation (Lekven et al, 1973).

In other animal experiments, the reduction of FFA uptake, favouring, therefore, glucose metabolism, resulted in the reduction of ischaemic damage (Mjøs, 1976), and the corollary was true when glucose metabolism was stimulated by dichloracetate and the degree of ST elevation was seen to be restricted (Mjøs et al, 1976).

The reduction of plasma FFA by pretreatment with p-chlorophenoxyisobutyrate is associated with a decrease in the myocardial extraction of FFA and with the reduction of the area of ischaemic injury (Mjøs et al, 1976).

Chest wall ST mapping in man has been used to show a reduction in ST depression in men exercised to the point of anginal pain, where the nicotinic acid analogue described later in this thesis was used to inhibit adipose tissue lipolysis and hence lower plasma FFA (Luxton et al, 1976).

Attempts to produce ventricular arrhythmias by elevating plasma FFA in experimental animals have produced conflicting information. Initial studies using the intravascular hydrolysis of triglycerides by heparin, with consequent release of FFA, were carried out in mongrel dogs. Elevation of FFA in the presence of AMI was frequently associated with an increased frequency of VPB and occasional ventricular tachycardia. This effect was reversible by Protamine Sulphate which prevented further lipolysis and lowered the plasma FFA. Arrhythmias occurred 20-30 minutes after peak FFA concentrations were reached, and further, it was shown that catecholamine infusion elevated FFA and produced arrhythmias which could again be modified by lowering the FFA with an analogue of nicotinic acid (Kurien and Oliver, 1971).

A second series of experiments in mongrel dogs (Kurien et al, 1971) confirmed these findings, but emphasised that the levels of

plasma FFA required to produce arrhythmias were in excess of those seen in man and that heparin itself may alter the composition of myocardial FFA. Albumin bound FFA was then produced with a similar FFA composition to that of dog plasma and it was infused to elevate the plasma FFA to levels seen in man with AMI. The initial experiments of this type confirmed the appearance of more arrhythmias in the treated than in the control group. A more extensive series, however, failed to support these findings and profound hypotension during the infusions, with its haemodynamic consequences, rendered the results inconclusive (Riemersma et al, 1974). Parallel experiments in 36 greyhound dogs and in a further 5 mongrel dogs did not support the earlier findings (Opie et al, 1971), although the same method of elevating FFA was used. Elevation of FFA to 6000 μEq/L and priming of the myocardium with lipid failed to produce any excess of arrhythmias. The complete absence of arrhythmias in these experiments has never been explained despite differences in experimental material. It is possible, however, that other factors which predispose to the development of arrhythmias were altered, such as higher heart rate, pericardiectomy and coronary artery ligation with interruption of the sympathetic nerve supply, and modification of local catecholamine concentrations. The same workers have, however, produced ventricular arrhythmias in isolated rat hearts using unbound FFA (Opie, 1970).

An alternative approach to the problem in a small series of experiments was that in which adipose tissue lipolysis was inhibited and the effect on the naturally occurring incidence of arrhythmias considered. A significant reduction in incidence of all VPB was recorded with antilipolytic treatment but a direct anti-arrhythmic effect of the drug could not be excluded (Smith and Duce, 1974).

SUMMARY

The accumulated experimental evidence from in vitro and in vivo work in animals indicates that FFA have a metabolic stimulant effect on the myocardium, and if present in excess in hypoxic conditions, can produce an increase in oxygen demand which cannot be met. FFA have been shown to increase MVO_2 in normal dog hearts and to decrease contractility in hypoxic conditions. This is accentuated when the FFA/albumin ratio exceeds 2:1 with a consequent rise in the amount of unbound FFA being presented to the myocardium. FFA also have been shown to increase the output of creatine kinase from the damaged myocardium, and the area of ST elevation produced by hypoxia alone. These effects can be partially ameliorated by inhibition of lipolysis by various agents and alteration in the relative amounts of FFA and glucose made available to the myocardium. This implies that FFA can play some part in determining the area of disturbance of membrane function, and, therefore, may influence the extent of the ischaemic damage.

Whilst this evidence mitigates firmly in favour of high concentrations of plasma FFA having adverse effects on infarct size and mechanical performance, the experimental evidence that FFA can cause ventricular arrhythmias is less decisive. The attempts to precipitate arrhythmias in dogs have been successful, but the FFA composition of the infusates and the very high plasma FFA levels achieved influences the interpretation of the results. Attempts to meet these criticisms were successful in that arrhythmias were apparently produced in a further series of animals, and whilst the arrhythmias were of the types seen in man, and were frequent, formal comparison with a control group failed to show a statistically significant higher incidence.

CHAPTER 5

The Clinical Relationship Between Elevated Plasma FFA and Arrhythmias in Man with Acute Myocardial Infarction

There is a marked rise in plasma FFA in patients with AMI. This was first described in 1966 (Kurien and Oliver, 1966) and has been confirmed by further studies (Gupta et al, 1969;Gupta et al, 1972;Hagenfeldt and Wester, 1973; Jadraque, 1972; Nelson, 1970; Oliver et al, 1968; Prakash et al, 1971; Ravens and Jipp, 1972; Reimann and Schwandt, 1971; Rutenberg et al, 1969; Sznajderman et al, 1973). Plasma FFA begin to rise within the first 30 minutes after the onset of symptoms and reach a peak in the region of 1200 μEq/L 1-2 hours later (Vetter et al, 1974). Levels then decrease towards normal by 24 hours after AMI, as shown in Figure 6. The clinical relationship between this rise in FFA and the complications of AMI was first suggested by Kurien and Oliver when death occurred in 3 patients in their study and all were observed to have FFA in excess of 1000 μEq/L. This included the patient with the highest FFA of all in the study (Kurien and Oliver, 1966). A subsequent study of 200 patients (Oliver et al, 1968) related each of the clinical complications of AMI to FFA concentrations. When plasma FFA $>$ 1200 μEq/L were recorded, a significantly higher number died early in the illness, and during the follow up period. A significantly greater number had serious ventricular arrhythmias or conduction defects in the presence of these levels of FFA. The finding of a relationship between elevated plasma FFA and ventricular arrhythmias was confirmed by Gupta (Gupta et al, 1969) in 35 patients but refuted by Rutenberg (Rutenberg et al, 1969) in 78 patients on the grounds that the admission FFA was not related to complications later in the illness. There was, however, "a decisive trend for FFA to be elevated at the time of death or when the patient first manifested premature

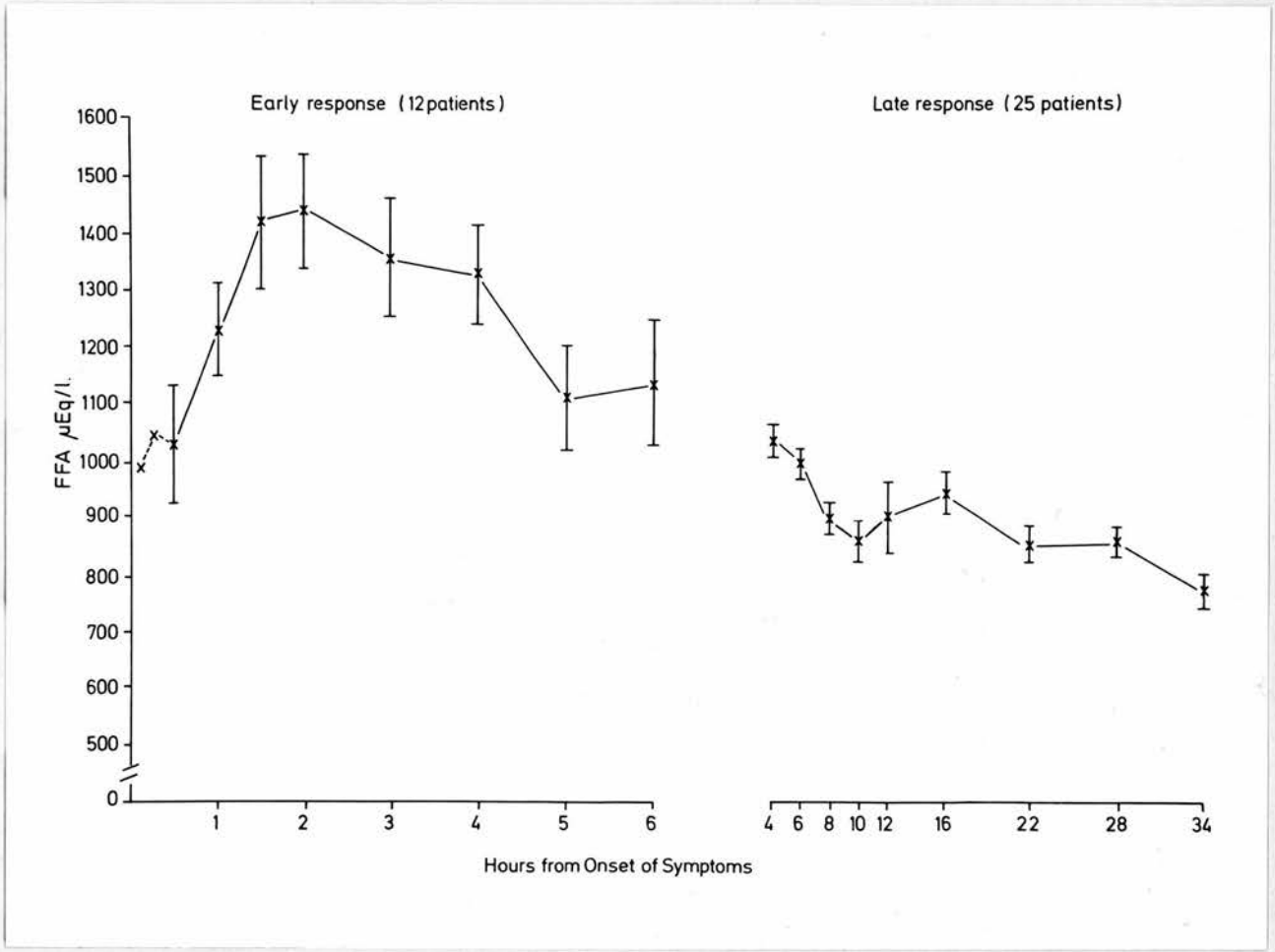


Figure 6. Plasma Free Fatty Acid Concentrations Following Acute Myocardial Infarction in Man.
(From Oliver, Rowe and Vetter in 'Effect of Acute Ischaemia on Myocardial Function').

atrial contractions, ventricular arrhythmias and heart block...." Subsequent analysis of this study using a dividing line of plasma FFA concentrations of 1200 μEq/L failed to confirm the earlier findings of Kurien et al (Rutenberg and Soloff, 1970).

The failure of admission FFA to predict complications was supported by Nelson, but no relationship with peak plasma FFA was attempted in the study and artificial elevation of FFA with heparin was not associated with the immediate onset of complications (Nelson, 1970).

Positive correlations between elevated FFA and complications of AMI were demonstrated by Prakash (Prakash et al, 1971) in 21 patients of whom 4 died, where FFA $>$ 1100 μEq/L were related to complications, and by Gupta (Gupta et al, 1972) where 8 of 60 patients died and all had marked elevation of plasma FFA. The mean plasma FFA concentrations in this group at the time of onset of complications was higher than that in the non-complicated group. Jadraque confirmed these findings (Jadraque, 1972) with the exception of a negative relationship between FFA concentrations and both heart block and supraventricular arrhythmias. As in later studies by Hagenfeldt (Hagenfeldt and Wester, 1973) the mean plasma FFA for the group was lower than usually observed. The study of Hagenfeldt is interpreted as contradictory to a relationship between FFA and serious arrhythmias. These results are, however, difficult to compare with previous studies as the FFA methodology differed, producing overall lower estimates of plasma FFA, and all arrhythmias were considered together without distinction into sub-groups. Only 3 patients had serious ventricular arrhythmias and there were no deaths. This suggests a selected group of relatively uncomplicated patients with lower plasma FFA. Even so, there was a positive correlation within this group between FFA and clinical severity including non-specific symptoms such as vomiting. Ravens and Jipp, in 1972, showed in 25 patients a trend towards high FFA with arrhythmic complications, and Sznajderman, in 1973,

in 70 patients showed higher FFA in complicated infarctions, and a longer duration of elevation of plasma FFA in the 14 patients who died. These studies are summarised in Table I.

SUMMARY

Numerous studies have shown a marked increase in plasma FFA concentrations in patients with acute myocardial infarction. The peak elevation occurs 1-2 hours after infarction and in those studies in which serial sampling was undertaken the peak appears to be in the region of 1200 μEq/L. Peak levels are maintained for a few hours only, and normal levels are achieved within 24 hours. The weight of clinical evidence is in favour of a positive relationship between the extent of the elevation of FFA and the occurrence of serious complications and death in the acute phase, and in the Oliver experience, with death in the later phase of the illness.

A complicated course and the appearance of ventricular arrhythmias is associated in most studies with plasma FFA concentrations on at least one occasion during the first 24 hours of greater than 1000 μEq/L, and in the case of subsequent death, levels in excess of 1100 μEq/L are commonly recorded. There is no evidence that a single measurement of FFA on admission to hospital can predict the clinical course of the illness in the individual. The type of complication related to high FFA is also variable, as Oliver found high levels in patients with cardiogenic shock, a finding so far unconfirmed, and directly contradicted by Rutenberg who found low FFA in the "Shock Syndrome" with poor peripheral perfusion. Oliver's finding of a relationship with A-V block is not confirmed by Jadraque. In most instances serious ventricular arrhythmias have been positively correlated with high FFA although it is necessary to be cautious in this interpretation because of the variable time periods over which the ECG was recorded, and the inconsistency of recording methods.

Table 1.

Clinical Studies of Relationship between Raised Plasma FFA Concentrations and Complications of Acute Myocardial Infarction in Man

Author	Number of Pts.	Number of Deaths	Support for Hypothesis That ↑ Plasma FFA = ↑ Complications of AMI in Man
Kurien and Oliver 1966	20	3	+ ve
Oliver, Kurien and Greenwood 1968	200	32	+ ve
Gupta 1969	35	0	+ ve
Prakash 1971	21	4	+ ve
Gupta 1972	60	8	+ ve
Jadraque 1972	50	8	+ ve
Sznajderman 1973	70	14	+ ve
Nelson 1970	24	0	- ve
Von Ravens and Jipp 1972	25	0	- ve
Hagenfeldt 1973	24	0	- ve

CONCLUSION TO PART II

There are two possible interpretations of this relationship between elevated plasma FFA and the complications of AMI.

The first is that the FFA elevation is merely a reflection of enhanced catecholamine activity, and that it is a result of various degrees of systemic metabolic disturbance due to the development of complications of differing severities.

The second interpretation is that the higher FFA elevations precipitate further local metabolic disturbance in the myocardium with consequent development of arrhythmic and other complications. None of the clinical or experimental observations so far described has distinguished between these two possibilities.

PART III

INTRODUCTION

The suppression of adipose tissue lipolysis in man with consequent lowering of the plasma FFA would provide a mechanism for the exploration of the hypothesis that elevated plasma FFA in acute myocardial infarction may cause ventricular arrhythmias.

Nicotinic acid is a known inhibitor of adipose tissue lipolysis and lowers the FFA in normal man for a period of two hours following a single oral dose of 500 mg. This lowering is followed by an acute rebound in FFA to levels often in excess of the initial concentration (Pereira and Mears, 1971). Nicotinic acid is not suitable for experimental use in patients with acute myocardial infarction, however, since it leads to peripheral vasodilation and hypotension, and an increase of 20-30% in cardiac output with an associated tachycardia (Carlson and Orö, 1962; Ekstrom-Jodal et al, 1970). The development of analogues of nicotinic acid has, however, dissociated to a considerable extent the antilipolytic effect of the parent substance from its haemodynamic effects, and the experimental work described in this thesis is based on the use of one such analogue of nicotinic acid which lowers raised plasma FFA in both animals and man, and has no significant haemodynamic effects.

Material

The analogue used was 5-fluoro-3-hydroxy-methyl-pyridine hydrochloride which is metabolised a 5-fluoro-nicotinic acid. The structures of nicotinic acid and some of its derivatives are shown in Figure 7.

It will be described in this thesis as a nicotinic acid analogue (NAA). Pharmacological testing has demonstrated that this NAA

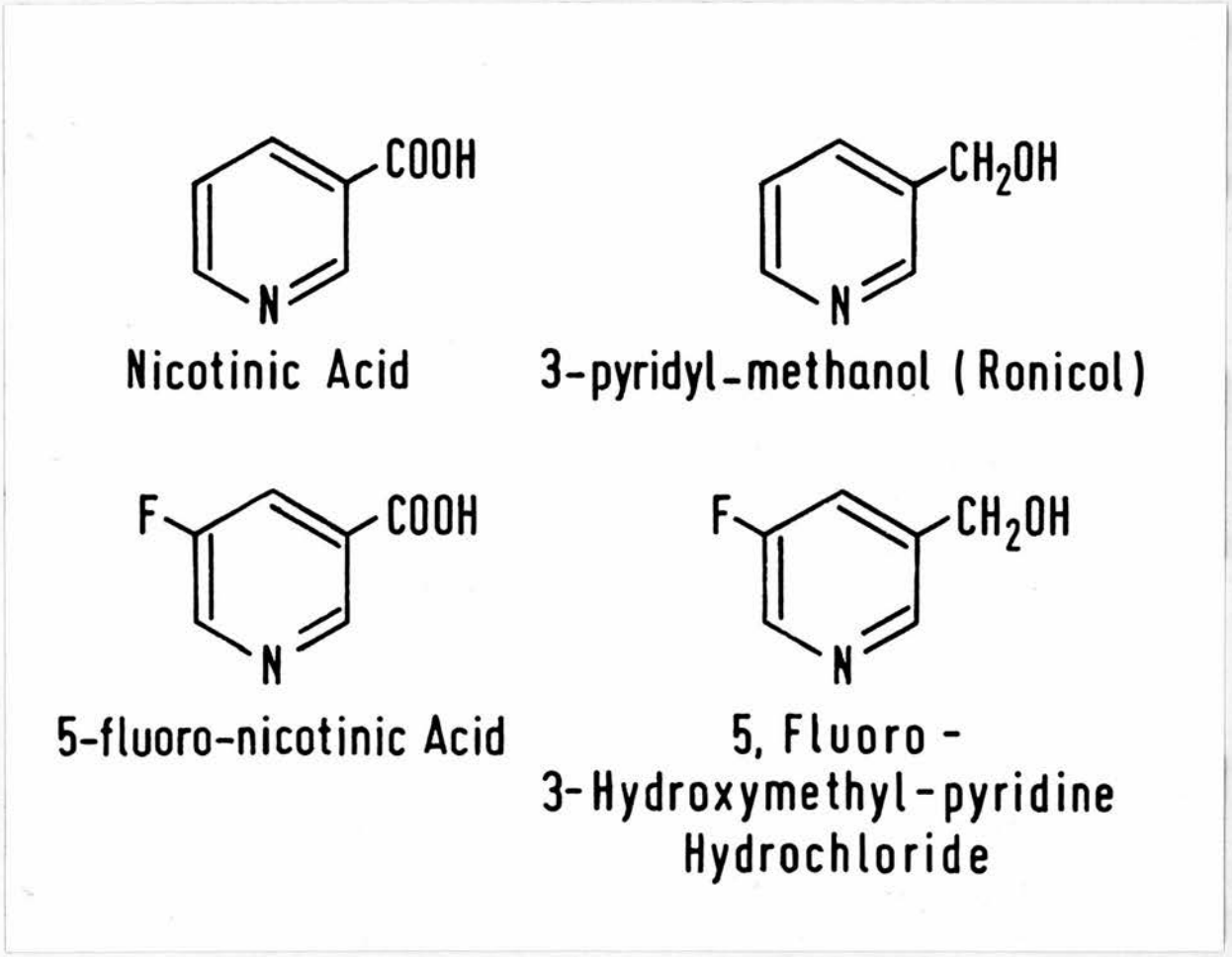


Figure 7. Structures of Nicotinic Acid and some derivatives.

would lower plasma FFA within 20 minutes of the administration of 200 mg of the base in an oral capsule, and maintain suppression of FFA for a period varying from 2 to 4 hours depending on the individual subject. In dogs, skin flushing was rare, and there was no increase in the hind leg blood flow.

Biochemical Methods

Throughout the work presented in this thesis, serial measurements were made of plasma FFA estimated by the Dole method using the Trout modification and two acid washes (Trout et al, 1960). The total catecholamines were measured by a tri-hydroxy-indole method (Carruthers et al, 1970) and blood glucose by an automated glucose oxidase method (Middleton and Griffiths, 1957). Plasma triglycerides were estimated by an automated method (Kessler et al, 1965) and in experiments with patients with acute myocardial infarction, the serum creatine kinase levels were measured by the method of Smith (Smith, 1967).

RESULTS

Effect of NAA on Healthy Men

The effect of the NAA on plasma FFA in normal men was assessed in 8 healthy, fasting, non-obese men, aged 24-47 years, and with a mean height-weight index of 1.85 (range 0.85-2.1). The subjects were rested for 30 minutes; venous blood was withdrawn twice during the resting period, and 200 mg of NAA was then given orally. Blood was then taken every 15 minutes, for 2 hours, and then at 3 and 4 hours after the administration of the drug.

Plasma FFA levels began to fall within 15 minutes of the administration of the NAA. See Figure 8.

Lowest levels were reached at 2 hours from the administration of NAA with a mean maximal fall for the group of 42% from the starting value (range 23-56%). The plasma FFA returned to pre-treatment levels by the fourth hour. The pulse rate (mean rate 65 beats per minute), blood pressure (mean systolic pressure 115 mm of mercury, mean diastolic pressure 69 mm of mercury) and blood glucose (mean 72 mg%) at the start of the study did not change throughout the experimental period of four hours. Four men had minor flushing of the skin restricted to the face about 12 minutes after taking the NAA and this faded in all cases within 2 hours.

Effect of NAA After Noradrenaline Infusion in Healthy Men

Sympathomimetic agents increase plasma FFA in normal men (Pilkington et al, 1966). In pilot studies sublingual isoprenaline produced unreliable FFA elevation, but i.v. infusion of isoprenaline, adrenaline and noradrenaline all produced more consistent results. Noradrenaline infusion produced consistently the highest FFA elevation, and this method was, therefore, used to study the effect

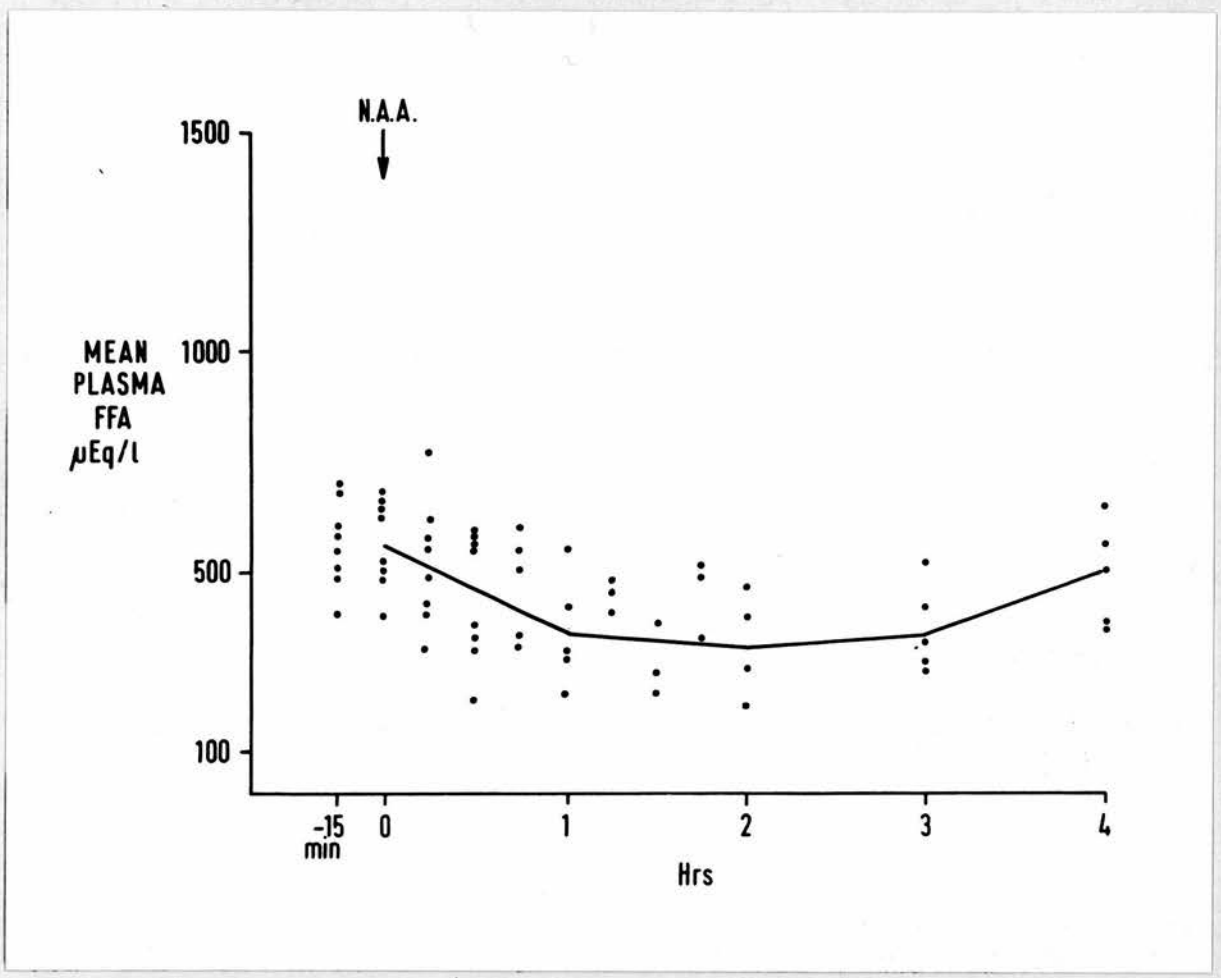


Figure 8. Changes in Plasma FFA concentration in 8 Normal Men after Oral Administration of 200mg. NAA.

of NAA on raised plasma FFA in normal men.

After an overnight fast, three normal healthy non-obese men, including the author, were rested for 30 minutes before the experiment. A 14G needle was used for sampling from the left antecubital vein, and its patency was maintained by a saline infusion. After 30 minutes a 14 gauge needle was introduced into the right antecubital vein for infusion of noradrenaline in saline over a period of 30 minutes, at a dose rate of 0.1 mg/Kg/minute. Blood samples were obtained every five minutes during the infusion, and at 10, 20 and 30 minutes after the end of the infusion. Each man acted as his own control, and was given, with an interval of a week, and in this order, noradrenaline in saline infusion alone, noradrenaline in saline infusion plus 200 mg oral NAA in a single dose, and noradrenaline in saline infusion plus 50 mg intravenous NAA, with the latter given as a single intravenous injection over 5 minutes.

Figure 9 shows that infusion of noradrenaline was followed within 10 minutes by a rise in plasma FFA, and this lasted until the end of the infusion when levels fell rapidly towards normal. The mean maximum level of FFA reached was 1663 μEq/L (range 1530-1800). Infusion of noradrenaline followed by 200 mg of oral NAA, given immediately after commencement of the infusion, showed that NAA curtailed the increase in plasma FFA. This effect was maintained despite the ongoing infusion and lasted until the end of the infusion period and for the subsequent 30 minutes. The effect of 50 mg of intravenous NAA given 15 minutes after the commencement of the infusion was similar. Blood glucose concentrations and plasma triglycerides remained within the normal limits and were unaffected by noradrenaline infusion or by NAA. Slight flushing occurred, restricted to the face, in one man on both occasions that the NAA was given. This was not associated with an increase in pulse rate.

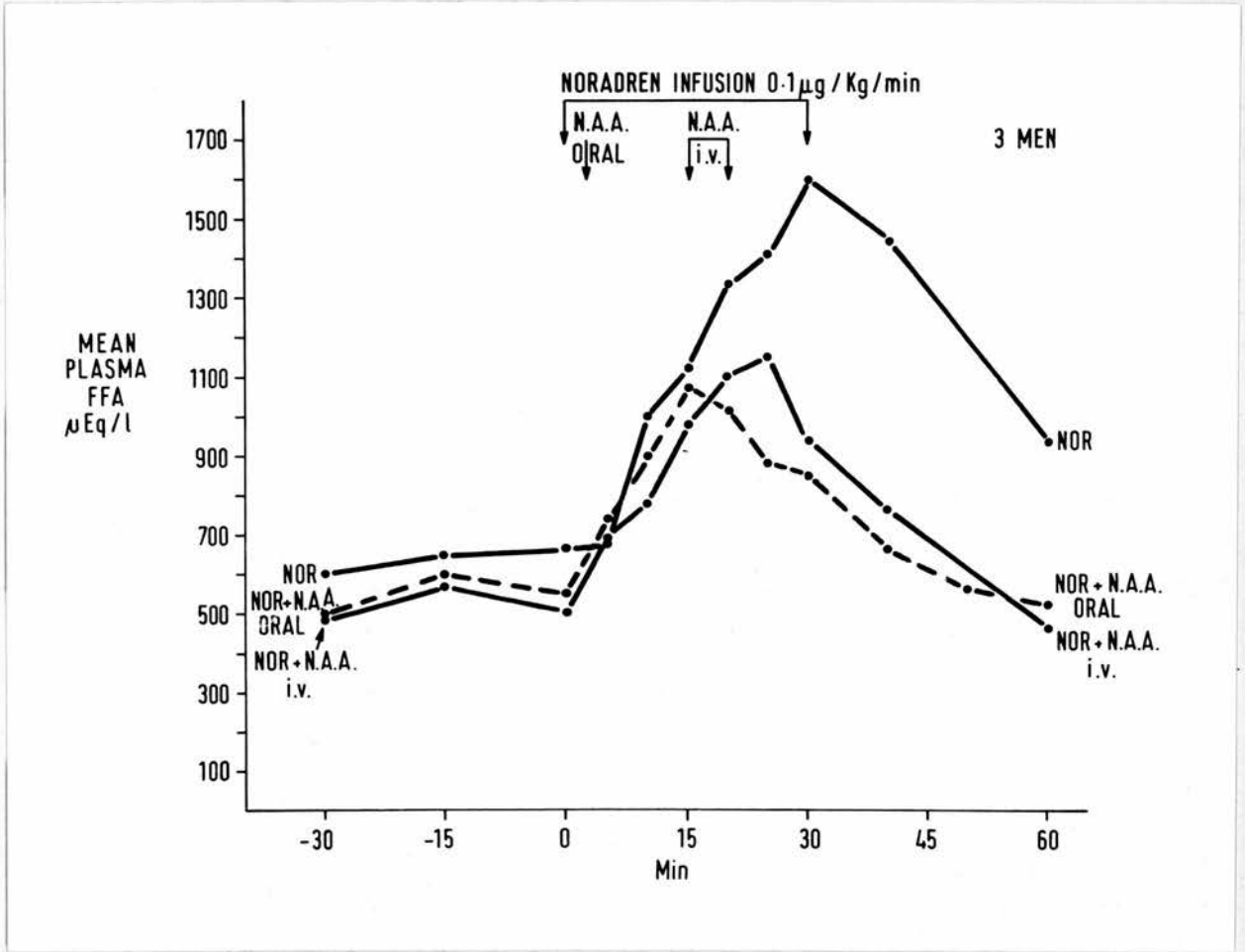


Figure 9. Effect of a single dose of NAA given orally (200 mg.) or intravenously (50 mg.) on Noradrenaline - induced elevation of plasma F.F.A.

Haemodynamic Effects of NAA in Patients with Acute Myocardial Infarction

Minor skin flushing has been described during the preceding studies of NAA in normal men, although this was not associated with a rise in pulse rate, or a fall in the blood pressure as measured by the sphygmomanometer cuff. These apparently minor changes were in keeping with the pharmacological evidence obtained in animals. Nevertheless, before proceeding to large scale investigations it was considered important to determine whether these effects would be magnified in patients who had recently suffered an acute myocardial infarction.

The haemodynamic effects of NAA on the systemic circulation were, therefore, investigated in 5 men with acute myocardial infarction. In all, the course of the infarction had been uncomplicated, and none of them had any medicaments within the 12 hours prior to the investigation. The study was performed 24-36 hours after the onset of symptoms of acute myocardial infarction with the informed consent of the patient. For continuous measurements of arterial blood pressure, a nylon cannula was placed percutaneously in the left brachial artery, and a long nylon catheter was introduced percutaneously through an antecubital vein into the superior vena cava. The arterial pressure was measured by means of an electro-mechanical pressure transducer (Statham P23DG) and the cardiac output by means of a dye dilution technique using indocyanin green ("cardiogreen").

The arterial pressure, cardiac output, and plasma FFA concentrations were recorded every 15 minutes for half an hour before and one hour after the oral administration of a single capsule containing 200 mg of NAA (see Figure 10).

The cardiac index (CI) fell slightly in 4 patients, and in 1 patient there was a slight rise. Maximal mean decrease in CI was 16%. This decrease was not related to the time of administration of the

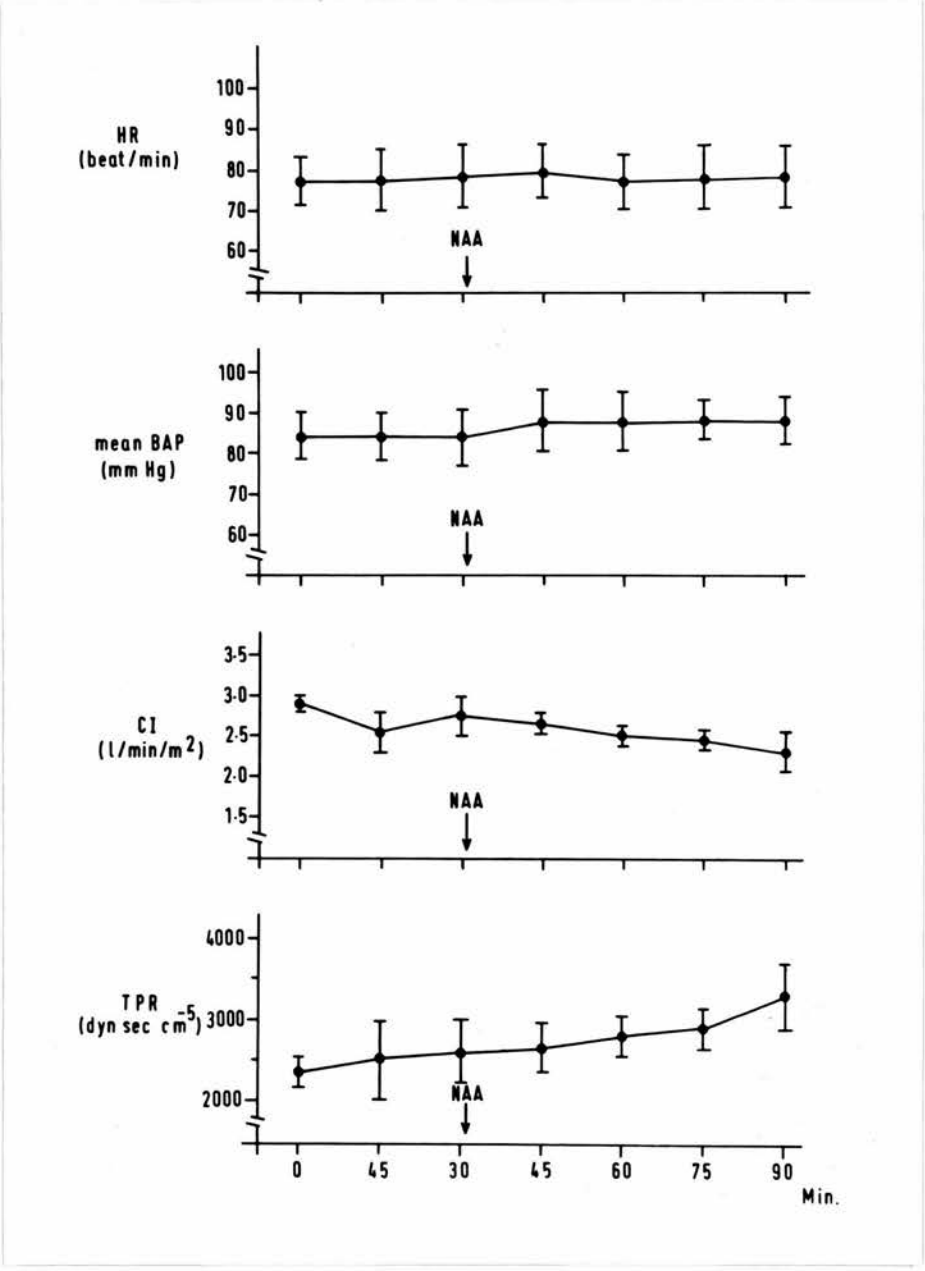


Figure 10. Haemodynamic effects (Mean $\pm$ S.E.M.) of a single oral dose of 200mg. of N.A.A. in five patients with myocardial infarction.

NAA and would be expected during serial estimations of the CI in resting patients becoming accustomed to the technique. The heart rate remained unchanged, the arterial pressure showed a maximal rise of 4 mm of mercury, and the stroke index did not change significantly. The rise in total peripheral resistance was related to the small change in CI. In all 5 patients left ventricular work decreased slightly and the mean maximal fall in left ventricular work was 14% for the whole group.

These five patients also showed a mean fall in plasma FFA concentration of 50% after they received NAA. Plasma total catecholamines were measured in 3 patients during these studies and were within the normal range and showed no change over the whole period of the experiment.

It was concluded, therefore, that when given to patients with acute myocardial infarction this NAA had no major haemodynamic effect which might endanger the patient or influence the outcome of a study of its effects on FFA in such patients.

Effects of NAA on Plasma FFA in Patients with Acute Myocardial Infarction

In this series of experiments and in all subsequent experiments with patients with acute myocardial infarction, informed consent was obtained from each patient for the administration of this substance which had no known serious side effects, and which at a later date might be shown to advantageously modify the outcome of acute myocardial infarction.

Pilot Study 1

To investigate the effect of NAA on raised plasma FFA concentrations in patients with acute myocardial infarction, patients were selected with electrocardiographic evidence of acute myocardial infarction sufficient to warrant allocation to Groups 1.1 or 1.2 of the Minnesota code (Rose and Blackburn, 1968). Clinical diagnosis was later confirmed by serum creatine kinase and aspartate amino-transferase levels. Diabetics, patients with cardiac failure, and those taking drugs which affect plasma FFA were not considered for entry into the study. Six patients admitted within 12 hours of the onset of symptoms, and with a plasma FFA of more than 1000 μEq/L were selected for this pilot study. The mean time between onset of symptoms and the commencement of treatment with NAA was later shown to be 9.0 hours, and the mean maximum FFA concentration before treatment was 1140 μEq/L.

An indwelling catheter with a teflon obturator was inserted into a forearm vein for intermittent blood sampling. 200 mg of NAA were given orally in capsule form every 4 hours for 72 hours (Group 1, Table 2). Plasma FFA and blood glucose levels were measured three times in the first 2 hours after starting treatment and on four occasions during the subsequent 4 days.

In all patients given NAA there was a steep fall in plasma FFA

Group	Sex		Mean time between onset and treatment (hr.)	Mean max. F.F.A. before treatment (μEq/l.)	Fall in mean F.F.A. in first 2 hr. after N.A.A. or placebo
	M	F			
1. N.A.A. 4-hourly	3	3	9	1140	54%
2. N.A.A. 2-hourly	5	1	7.25	1400	58%
3. Placebo	5	3	8	1290	2%

Table 2.

COMPARISON OF THREE GROUPS OF PATIENTS TREATED WITH N.A.A. AND PLACEBO

in the first hour, reaching a nadir during the first 2 hours. The mean maximum fall within the first 2 hours was 54% from the starting value (range 40-66%). After the initial fall, however, control of FFA concentration was unreliable, even within the first 24 hours of starting treatment with NAA. In 3 out of the 6 patients control of FFA was maintained below 1000 μEq/L in the first 24 hours. In the remainder, however, plasma FFA returned to 1000 μEq/L or more, at least once in the first 24 hours.

For contrast, the plasma FFA changes were studied in 8 other patients with acute myocardial infarction who were selected in the same way and given identical placebo capsules on a double blind basis (Group 3, Table 2). The plasma FFA in this control group followed a similar pattern to that previously reported. The mean maximum fall in plasma FFA within the first 2 hours of treatment with placebo was 2% from the starting level.

The blood glucose levels showed no consistent change during the treatment period. There was no flushing, or other side effect.

Pilot Study II

Because plasma FFA were not maintained at normal levels in all patients throughout the first pilot study, and escape from control appeared to occur for the first time between two and four hours from the start of treatment, a further six patients with acute myocardial infarction were given 200 mg NAA 2 hourly for 48 hours. The selection of patients was the same, and the patients studied were comparable to those in the previous group (Group 2, Table 2). Figure 11 shows that all patients in this group had a steep fall in plasma FFA in the first hour, again reaching a nadir within 2 hours. The mean maximal fall within the first 2 hours was 58% and control of plasma FFA was maintained in all patients for 24 hours around a level of 500 μEq/L. This was followed by a rise to approximately 600 μEq/L at 48 hours. The mean maximum FFA concentration

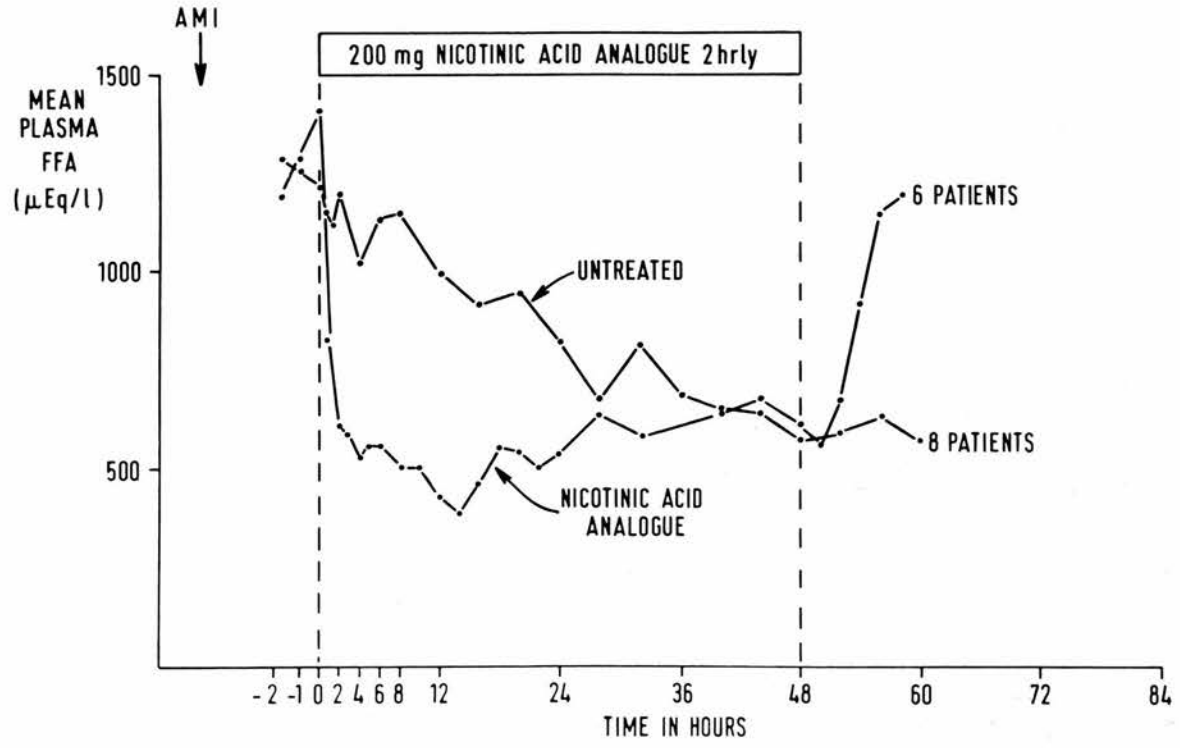


Figure 11. Effect of 200mg. of oral N.A.A. or placebo given 2-hourly for 48 hrs. in 14 patients with Acute Myocardial Infarction.

before treatment was 1400 μEq/L and the mean time between onset of symptoms and commencement of treatment with NAA was 7.25 hours (See Table 2). Again, there was no consistent change in blood sugar. There was no relationship in this, nor in the previous group of patients between the body weight and the success of control of FFA. The body weights ranged from 45-90 Kg.

During therapy with NAA there was no flushing or adverse side effect. Within 4 hours of the withdrawal of NAA there was a rapid increase in the plasma FFA concentrations towards pretreatment levels. These were exceeded in some cases within 12 hours of stopping therapy. This rebound phenomenon commonly occurs after FFA suppression by other means, and in these pilot experiments was not accompanied by any adverse features.

Conclusions from Pilot Studies

These observations indicate that this NAA which is metabolised as 5-fluoro-nicotinic acid, has a similar effect on plasma FFA concentration to that reported elsewhere with nicotinic acid. Presumably it achieves this effect by a similar suppression of adipose tissue lipolysis. Unlike nicotinic acid, however, it rarely produces skin flushing and in those situations in which skin flushing is seen it is mild, and commonly confined to the face. It has no significant haemodynamic effects as judged by clinical observation in normal men, and by formal haemodynamic investigation in patients with acute myocardial infarction. It is orally active in doses of 200 mg if given every 2 hours, but control of FFA is unreliable with a less frequent dosage regime.

A Double Blind Trial of The Effect of NAA on Plasma FFA and Ventricular Arrhythmias in Patients with Acute Myocardial Infarction

A double blind trial of NAA was conducted in patients admitted to a coronary care unit (CCU) with a clinical diagnosis of myocardial infarction. All had severe praecordial pain starting 12 hours or less before admission to the trial; those in whom the time of onset of symptoms was doubtful were excluded. All patients with electrocardiographic evidence of infarction leading to classification as Group 1.1 and 1.2 of the Minnesota code were initially accepted into the trial. The diagnosis of fresh myocardial infarction was later confirmed by increased serum creatine kinase (CK) concentrations. Patients with normal CK were excluded after completion of treatment but before analysis of the results. The following groups of patients were excluded from admission to the trial: those with cardiogenic shock or overt cardiac failure; those taking drugs known to affect plasma FFA such as antilipolytic agents, or beta adrenergic blocking drugs; and those with diabetes mellitus, hypothyroidism treated with thyroxine, and hypertension treated with methyl dopa. During the trial period, morphine, diazepam, digoxin, diuretics and other drugs were given to patients where indicated, but anti-arrhythmic drugs were only given after serious ventricular arrhythmia had been observed by the routine monitoring procedure. Thus the initial frequency of a ventricular arrhythmia could not have been affected by orthodox anti-arrhythmic treatment or prophylaxis, and the system used for the monitoring of ventricular arrhythmias during the study was not used as a basis for routine anti-arrhythmic treatment.

Informed consent for administration of the NAA and the withdrawal of blood samples was sought from 82 patients, and 81 agreed to enter the study. They were not consecutive admissions to the CCU because the number of laboratory analyses made this impracticable, but no regular omissions took place such as those admitted during the nights or at week-ends. Consequently the mean age and sex of the groups studied resembled those of routinely admitted patients, and the distribution of admissions by time of day was also as expected from admissions to the CCU in the previous year.

Eleven patients were excluded from the overall analysis of the results: 4 because the ECG tape recorder failed; 3 because of incomplete therapy; 3 because myocardial infarction was not confirmed; and one patient died early in the course of the study. A maximum of 70 patients was, therefore, included in the overall analysis, and the patient who died is described separately. All 81 patients initially admitted to the study were randomly allocated to treatment with NAA or placebo and of the 70 patients finally analysed, 34 had been given NAA and 36, placebo capsules.

One capsule of 200 mg of NAA or an identically prepared placebo was given 2 hourly for 24 hours, starting 15 minutes after the first blood sample. Blood samples were taken at the start of treatment; 1 hour later and at 4, 12, 20, 24, 32, 40 and 48 hours.

METHODS

Biochemical

In all patients, serial measurements were made of plasma FFA, plasma triglycerides, blood glucose, plasma total catecholamines, and creatine kinase, as previously described.

Assessment procedure for Ventricular Arrhythmias

Continuous magnetic tape recording of the ECG was started on admission and was continued for 48 hours from the time of administration of the first trial capsule. Later analysis of the tape recording was carried out without knowledge of the treatment group to which the patient had been allocated. The record was replayed for visual scanning on a 10 line Raster display oscilloscope at 60 times normal speed. The type of display used is illustrated in Figure 12. The number of isolated ventricular premature beats (VPB); episodes of 4 or more consecutive VPB; and episodes of ventricular fibrillation were counted. All episodes of 4 or more consecutive VPB were printed on to paper and the rate measured for classification as ventricular tachycardia where the overall rate was greater than 100 beats per minute. A special hybrid computer was used for counting when the VPB rate was too high for visual counting. The computer was also programmed to locate all VPB with coupling intervals of 400 milliseconds or less, and these were then printed on to paper for identification of R upon T or R upon apex T phenomena. While the computer scan was in progress, the ECG was displayed visually to check that the signals counted by the computer were individual VPB. R upon T ectopic beats were subdivided into ectopic R waves interrupting preceding sinus T waves (S/V type of R upon T) and ectopic R waves interrupting preceding ventricular ectopic T waves (V/V type of R upon T), as described by Smirk and Palmer. The R upon apex T was described as an R wave falling within 40 milliseconds of the visually located apex of the preceding T wave. Examples of these types of T wave interruption as recorded in this study as shown in Figure 2, Page 12

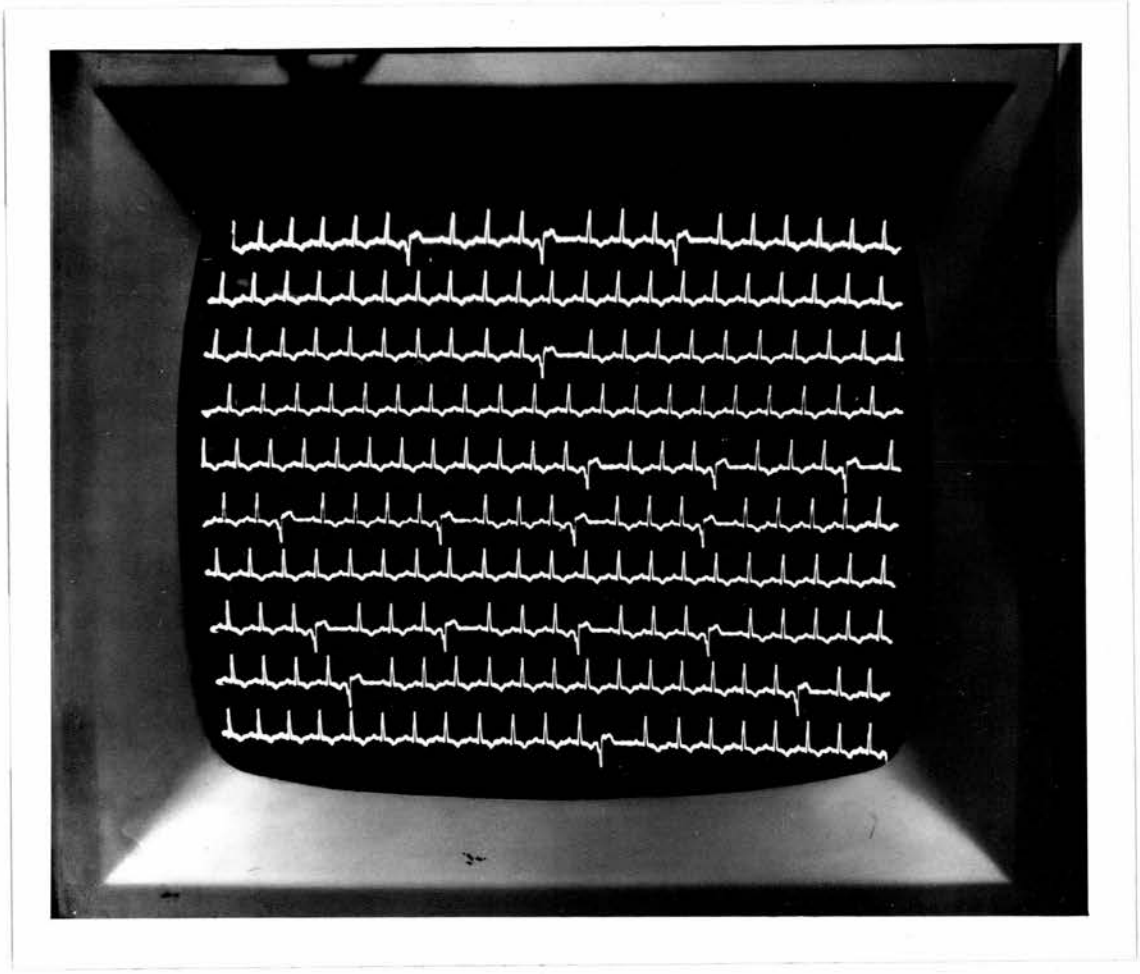


Figure 12. 10 Line Raster display unit as used for initial visual scan of all E.C.G. tape recordings.

Assessment Procedure for Adequacy of FFA Control

The pilot studies with NAA on man with acute myocardial infarction suggested that whilst NAA reliably produced a steep initial fall in FFA the extent of subsequent control during the remainder of the treatment period might not be so reliable. Consequently an arbitrary definition was required of the adequacy of FFA control achieved on this study. "Adequate" control of FFA by this NAA was arbitrarily defined, therefore, as reduction of FFA into the normal range (less than 800 μEq/L) at 12 and 20 hours after commencing treatment, and failing to reduce FFA into the normal range at these times was defined as "inadequate" control. More stringently, "good" control was arbitrarily defined as a 50% fall at 4 hours after the start of treatment plus normal concentrations maintained at 12 and 20 hours. Failure to achieve a 50% fall at 4 hours or to maintain FFA within the normal range at 12 and 20 hours after a 50% fall at 4 hours was classified as "poor" control.

Results of Double Blind Trial

Adequacy of Selection and Randomisation Procedure:-

The mean age of the two groups did not differ significantly, being 56.9 years for the NAA group (Range 40-72) and 55.3 years for the placebo group (Range 35-69). There was a similar distribution of the sexes between the two groups. The NAA treated group was admitted significantly later (5.7 hours) than the placebo group (5.3 hours). ($p = <0.01> 0.005$). This difference results from a skew distribution of patients admitted in the earliest hours. Of 11 patients admitted between 4 and 4.75 hours from the onset of symptoms, 9 were allocated to the NAA treated group compared with only 2 to the placebo group; and 3 patients admitted between 2.25 and 2.75 hours from the onset of symptoms in the NAA treated group compares with 7 admitted in the same period to the placebo group.

Although there were rather more inferior myocardial infarctions in the placebo group, (NAA group, 17/34, Placebo group 22/36) the site of the infarction did not differ significantly between the two groups. ($x^2 = 0.4825$ 1.d.f. = NS). The mean maximum FFA concentration before treatment was 1179 μEq/L in the NAA group and 1191 μEq/L in the Placebo group. These concentrations did not differ significantly (p = NS) and were consistent with a group of patients which did not include any cases with cardiogenic shock or frank cardiac failure. (Information concerning weight at the time of admission was not obtained from all patients. The mean body weight for 17 patients in the N.A.A. treated group was 70 Kgm, and that for 14 patients in the placebo group was 71.35 Kgm. p = NS.)

Plasma F.F.A. Control Achieved.

There was reduction in plasma F.F.A. in all 34 patients receiving the N.A.A. (Figure 13); 24 were adequately controlled, and 10 were inadequately controlled. Sixty per cent of patients had a fall of 50% or more in plasma F.F.A. within 4 hours of starting N.A.A., although early reduction into the normal range was not reliably achieved if the initial plasma F.F.A. level was greater than 1600μ Eq/L. The pattern of maintained reduction of F.F.A. was, however, variable, and applying the previously described alternative and more stringent assessment of F.F.A. control, only 16 of the 34 patients were shown to have good control. In these there was a steep initial fall of 50% of initial plasma F.F.A. within 4 hours with reduction into the normal range for the remainder of the treatment period; in the remaining 18 patients the plasma F.F.A. were poorly controlled.

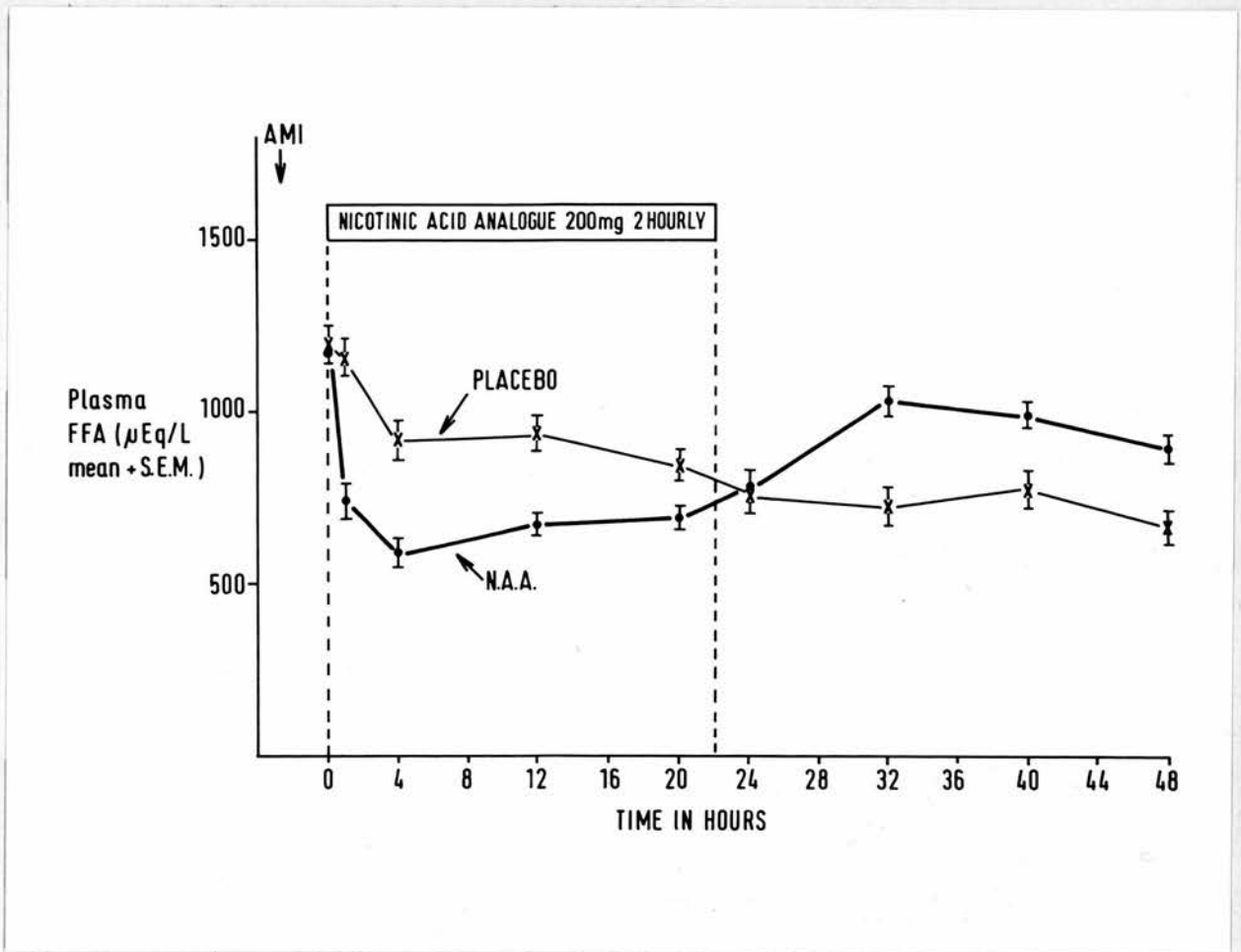


Figure 13. Plasma Free Fatty Acid Concentrations During Double Blind Trial.

The Incidence and Nature of Ventricular Arrhythmias:-

A total of 29,850 ventricular premature beats were recorded of which 1,871 had coupling intervals <400m. seconds, 489 were R/T and 131 were R upon Apex T. There were 139 episodes of ventricular tachycardia and 2 episodes of ventricular fibrillation.

The first recorded episode of each ventricular arrhythmia after entry into the trial has been used to define the "patient incidence" of that arrhythmia. The total number of arrhythmic events in each patient will not be described, because orthodox anti-arrhythmic drugs were given once an arrhythmic event was noticed by the routine monitoring procedure and may, therefore, have influenced the subsequent incidence of any arrhythmia.

1) Ventricular Fibrillation:-

Ventricular fibrillation (V.F.) developed in 2 patients, one from each treatment group, and plasma F.F.A. exceeded 1000 μEq/L in both cases at the time of onset of V.F. The N.A.A. treated patient developed V.F. 3 hours, and placebo-treated patient 2.25 hours after the start of treatment. Despite the fact that F.F.A. concentration was falling rapidly, in neither case had the F.F.A. fallen by 50% of the starting concentration, nor had the F.F.A. reached the normal range by the time V.F. occurred.

2) Ventricular Tachycardia:-

Ventricular tachycardia (V.T.) was defined as 4 or more consecutive V.P.B. with an overall rate greater than 100/minute. The number of patients in the whole N.A.A. and whole placebo treated groups having ventricular tachycardia on one or more occasion did not differ. In the N.A.A. group 19/34 had V.T. and in the placebo group 22/36 had V.T. (p = N.S.) In patients treated within 5 hours of the onset of symptoms, there were fewer patients having V.T. amongst those given the N.A.A., but this trend was not statistically significant. (See Fig. 14)

When the incidence of V.T. was related to the degree of F.F.A. control achieved however, important differences appeared (Table 3.)

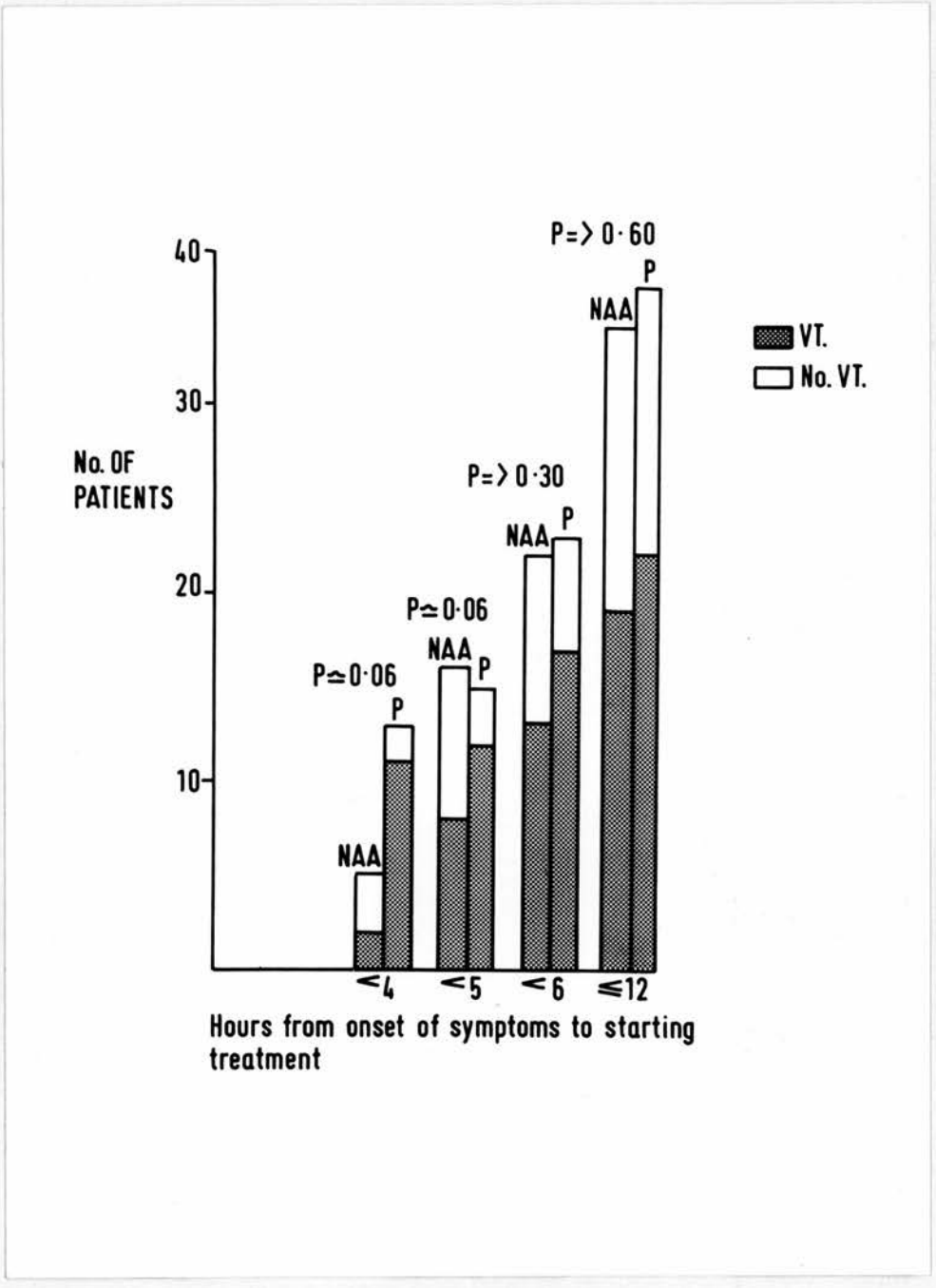


Figure 14. Cumulative Totals of Patients Having Ventricular Tachycardia.

In patients first treated within 5 hours of the onset of symptoms there was a significant difference ($p = <0.01$) in the number with V.T. when serum F.F.A. levels were reduced to within the normal range (=800ueq. per litre) at 12 and 20 hours after starting treatment with N.A.A. (adequate control) when compared with those in whom this degree of control was not achieved (inadequate control) (Table 3). There was also a highly significant difference ($p = <0.003$) in the number of patients with V.T. in those with good as compared with those with poor control (Table 3). No patient with good control of F.F.A. had V.T. The number of patients with V.T. in the placebo group did not differ significantly from those with poor control of F.F.A. given N.A.A.

It was clear that the mean times of admission to the trial of these N.A.A. and placebo sub groups were significantly different. (placebo= 2.7 hours: N.A.A. group = 3.8 hours, P = 0.001, for patients admitted within 5 hours of onset of symptoms.)

There was no difference between the number of patients with V.T. in those first treated between 5 and 12 hours from the onset of symptoms with N.A.A. or placebo. There were more patients with V.T. in the N.A.A. treated group with adequate control of F.F.A. (Table 3) when compared with those with inadequate control ($p = <0.05$) It was also noted that the mean times of admission to the trial were different in these sub-groups (adequate control = 6.2 hours: inadequate control = 8.5 hours, $p = 0.05$, in patients admitted between 5 & 12 hours from onset of symptoms). There was no significant difference in the numbers with V.T. in the good and poor control groups (Table 3). The 5 - 12 hour placebo group showed less V.T. (10/21) than the pre-5 hour placebo group (12/15). There was only one patient in the whole placebo group whose changes in F.F.A. resembled those in the N.A.A. good-control group, and statistical comparison of these groups was not therefore possible.

Table 3.
Number of Patients with V.T. related to degree of control of Plasma-F.F.A. in patients with Myocardial Infarction treated with N.A.A. or Placebo.

Start of treatment	NAA			Placebo		
	Total No.	No. with V.T.	Significance	Total No.	No. with V.T.	Significance
Pre 5 hr:						
Undifferentiated (i.e. whole group)	16	8	—	15	12	N.S.
FFA adequate control (< 800 μEq/L at 12 and 20 hr)	11	3	P<0·01	5	4	N.S.
FFA inadequate control (> 800 μEq/L at 12 or 20 hr)	5	5		10	8	
FFA good control (> 50% fall at 4 hr and < 800 μEq/L at 12 and 20 hr)	6	0	P<0·003	1	1	N.S.
FFA poor control (< 50% fall at 4 hr or > 800 μEq/L at 12 or 20 hr)	10	8		14	11	
5-12 hr:						
Undifferentiated (i.e. whole group)	18	11	—	21	10	N.S.
FFA adequate control (< 800 μEq/L at 12 and 20 hr)	13	10	P<0·05*	4	0	N.S.
FFA inadeqaute control (> 800 μEq/L at 12 or 20 hr)	5	1		17	10	
FFA good control (> 50% fall at 4 hr and < 800 μEq/L at 12 and 20 hr)	10	7	N.S.	0	0	—
FFA poor control (< 50% fall at 4 hr or > 800 μEq/L at 12 or 20 hr)	8	4		21	10	—

* This increased number of patients with V.T., when F.F.A. were adequately controlled, may be related to a significant difference in the times of admission to the study (6·2 hours in the adequately controlled group and 8·5 hours in the in adequately controlled group (P<0·05).

Time of Onset of V.T. from Start of Treatment:-

The mean time of onset of V.T. in the Pre-5 hour placebo group was 7.9 hours, and in the N.A.A. treated group was significantly earlier at 3.5 hours. ($p = < 0.05$). (See Table 4).
When related to the degree of F.F.A. control in patients treated within 5 hours of the onset of symptoms the mean time of onset of V.T. in the N.A.A. "poor control" group was 3.5 hours compared with 7.6 hours in the equivalent placebo group. (There was no V.T. in the good-control group). With respect to adequate control; the mean time of onset in the N.A.A. patients with adequate control was 2.6 hours, and was 4 hours for the group with inadequate control, compared with 5.7 hours and 8.6 hours for the respective placebo groups.

For the patients treated between 5 and 12 hours from the onset of symptoms, the mean time of onsetof V.T. was 8.2 hours in the placebo group compared with 7.4 hours in the N.A.A. treated group. (p = N.S.) With respect to the degree of F.F.A. control, those patients with good F.F.A. control had a mean time of onset of 9.1 hours, but there was no comparable placebo group. Those with poor F.F.A. control had a mean time of onset of 4.25 hours compared with that of 8.2 hours for the comparable placebo group.

With respect to adequate control in patients treated 5 to 12 hours after the onset of symptoms the mean time of onset of V.T. was 8.0 hours and in the comparable placebo group was 8.2 hours. Further subdivision was not possible because of the small numbers of patients involved (see Table 3).

Table 4.

Mean Time (hrs.) of Onset of V.T. after starting treatment

	NAA	PLACEBO	Significance
Pre 5 hours Whole group	3.5	7.9	p = <0.05
Good Control Poor Control	-) 0 3.5)	11 (1pt)) 0 7.6)	0 p = N.S.
Adequate Control Inadequate Control	2.6) p = N.S. 4.0)	5.7) p = N.S. 8.6)	p = N.S. p = N.S.
Post 5 hours Whole group	7.4	8.2	p = N.S.
Good Control Poor Control	9.1) p = N.S. 4.25)	-) 0 8.2)	0 p = N.S.
Adequate Control Inadequate Control	8.0) 0 -)	8.2) 0 -)	p = N.S. 0

Number of beats in Each Episode of Ventricular Tachycardia

The number of beats in each episode of V.T. is illustrated in Table 5. The majority of patients had ventricular tachycardia of less than ten beats per episode and episodes of eleven beats or more were rare. There were similar numbers of patients in both N.A.A. and placebo treated groups who had episodes of V.T. of 4 or 5 beats and 6-10 beats per episode.

Incidence of Ventricular Tachycardia with Short Coupling Intervals

Ventricular tachycardia of rapid overall rate and irregular coupling intervals including those where the ventricular R wave falls close to or on the T wave of a preceding beat has been described as a common precursor of ventricular fibrillation. The incidence of V.T. which included at least one coupling interval of less than 400 milliseconds is shown in Table 6. The overall numbers of patients in the N.A.A. and placebo treated groups having V.T. with short coupling intervals on one or more occasions did not differ. In patients treated within 5 hours of the onset of symptoms there were fewer patients having V.T. with short coupling intervals amongst the N.A.A. group (4/15) than in the placebo group (9/14). The incidence of this type of V.T. appeared to be related to the degree of F.F.A. control. The group with adequate control of F.F.A. had less of this type of V.T. (1/11) than the group with inadequate control of F.F.A. (3/4)($p=0.066$) Similarly there was less V.T. with short coupling intervals in the group with good control of F.F.A. (0/6) than in the group with poor control of F.F.A. (5/9) ($p = 0.084$). The group treated between 5-12 hours from the onset of symptoms showed no difference in the incidence of this type of V.T. when the whole N.A.A. treated group was compared with the whole placebo group. When the degree of F.F.A. control is considered, no differences were demonstrated between the subgroups with the different degrees of F.F.A. control. In the placebo group, however, there was more V.T. with short coupling intervals in the group with the equivalent of inadequate control of F.F.A. (7 / 17)

compared with the group with the equivalent of adequate control of F.F.A. (0/3). There appeared therefore, to be a trend towards a relationship between F.F.A. control and the incidence of this type of V.T. but it did not reach statistical significance.

Plasma F.F.A. concentrations related to the Onset of Ventricular Tachycardia

There was no significant relationship between the admission F.F.A. concentration and the incidence of ventricular tachycardia in either the N.A.A. treated group or the control group. (See Table 7) There was no relationship between the onset of the initial episode of V.T. and changing F.F.A. concentrations.

No of beats in each episode of
Ventricular Tachycardia

Table 5

	Number of Beats			
	$\leqslant 5$	6 - 10	11 - 15	16+
N.A.A. 0 - 5 Hrs. group	6	4	0	1
5 - 12 Hrs group	6	7	1	3
PLACEBO 0 - 5 Hrs. group	9	8	2	2
5 - 12 Hrs group	8	7	2	0

Table 6.
Number of patients with V.T. with coupling intervals ⩽400msecs. related to the degree of control of plasma-F.F.A. in patients with Myocardial Infarction treated with N.A.A. or placebo.

Start of treatment	NAA			Placebo		
	Total No.	No. with V.T. <400msecs	Significance	Total No.	No. with V.T. <400msecs	Significance
Pre 5 hr:						
Undifferentiated (i.e. whole group)	15*	4		14*	9	N.S.
FFA adequate control (< 800 μEq/L at 12 and 20 hr)	11	1	p = 0·066	5	3	N.S.
FFA inadequate control (> 800 μEq/L at 12 or 20 hr)	4	3		10	6	
FFA good control (> 50% fall at 4 hr and < 800 μEq/L at 12 and 20 hr)	6	0	p = 0·084	0	0	—
FFA poor control (< 50% fall at 4 hr or > 800 μEq/L at 12 or 20 hr)	9	5		14	9	
5-12 hr:						
Undifferentiated (i.e. whole group).	18	10		20*	7	N.S.
FFA adequate control (< 800 μEq/L at 12 and 20 hr).	13	8	p = 0·76	3	0	N.S.
FFA inadeqaute control (> 800 μEq/L at 12 or 20 hr)	5	2		17	7	
FFA good control (> 50% fall at 4 hr and < 800 μEq/L at 12 and 20 hr).	10	7	p = 0·36	0	0	—
FFA poor control (< 50% fall at 4 hr or > 800 μEq/L at 12 or 20 hr)	8	3		20	7	

* Totals reduced by one compared with table 3, of all V.T., because E.C.G. tape of inadequate quality for perfect analysis.

		Pre Treatment Plasma F.F.A. Concentration	
		F.F.A. $\geqslant$ 1,000 μEq/L	F.F.A. $<$ 1,000 μEq/L
N.A.A. 34 pts.	V.T.	13	6
	°V.T.	12	3
Placebo 36 pts.	V.T.	16	6
	°V.T.	10	4

Table 7

Relationship of Ventricular Tachycardia to Pre-treatment Plasma F.F.A. Concentrations.

Ventricular Premature Beats:-

All patients in the N.A.A. treated group and the placebo treated group had V.P.B.'s during the course of the recording. The highest total V.P.B. counts were greater than 1000 per 24 hours and tended to occur in those patients admitted earliest.

The incidence of various types of V.P.B. is demonstrated in Tables 8 - 13. The quality of the electromagnetic tape recording was poor in one patient in the N.A.A. group and in 2 in the placebo group, and precluded detailed analysis of the types of V.P.B. The tables therefore refer to 33 patients treated with N.A.A. and 34 treated with placebo.

When all V.P.B. of R/T type are considered together (Table 8) there was no significant difference in patient incidence between the N.A.A. and placebo groups when these were compared for the whole study, nor did sub-division into subgroups admitted between 0 and 5 hours and those admitted between 5 and 12 hours from the onset of symptoms affect the patient incidence of all types of R/T V.P.B. The degree of control of F.F.A. in the group admitted within 5 hours did not influence the incidence, although in the "5 - 12 hour" group there appeared to be more R/T V.P.B. in the group with good control of F.F.A. when compared with the group with poor F.F.A. control (p = N.S.) The same trend was apparent in those with adequate control of F.F.A. compared with those with inadequate control of F.F.A (p = N.S.) There were no significant differences between the whole groups or any of the subgroups when the R/T phenomenon of sinus T waves interrupted by ventricular R waves (R/T S/V) were considered. (See Table 9)

When R/T of the types where the ventricular R wave interrupted a preceeding ventricular T wave were considered (R/T V/V), there were no significant differences between the whole groups nor between the subgroups admitted between 0 and 5 hours, and those admitted between 5 and 12 hours from the onset of symptoms; (See Table 10) Nor did the degree of F.F.A. control in the pre 5 hours group influence the incidence of R/T V/V V.P.B. There was, however, a significantly higher incidence of all R/T V/V V.P.B. in the 5-12 hour group where those with good control of F.F.A. were compared with those with poor control of F.F.A. (p = 0.032.)
The same trend was present in those with adequate control compared with those with inadequate control. (p = N.S.)

There was a significantly lower incidence of all R upon apex T (R/apex T) phenomema in the pre 5 hours N.A.A. treated group (4/15) when compared with the pre 5 hours placebo treated group (10/14) (p = 0.02) (See Table 11) This difference was not however related to the degree of F.F.A. control. The incidence of all R/apex T phenomena was not influenced by the degree of F.F.A. control in the patients admitted between 5 and 12 hours.

When the numbers with R/apex T of V/V type are considered (See Table 12), the numbers in the N.A.A. treated group (2/15) are significantly less than those in the placebo treated group (8/14) (p = 0.02). There was only one incident of R/apex T of V/V type in each of the 2 patients in the treated group, and there were 19 incidents in the 8 patients in the placebo treated group. No patients had R/apex T V/V V.P.B. in the N.A.A. good control group; the 2 patients with R/apex T V/V V.P.B. being in the group with poor control. In the 5-12 hour group there was a trend towards a higher incidence of R/apex T V/V V.P.B. in the group with adequate control compared with the group with inadequate control.

The incidences of R/apex T of S/V type V.P.B. was also examined and no significant differences were found between any of the whole groups nor any of the subgroups. (See Table 13)

Table 8.

Number of patients with any type of R/T V.P.B. related to degree of control of Plasma-F.F.A. in patients with Myocardial Infarction treated with N.A.A. or placebo.

Start of treatment	NAA			Placebo		
	Total No.	No. with R/T	Significance	Total No.	No. with R/T	Significance
Pre 5 hr:						
Undifferentiated (i.e. whole group)	15	12	-	14	13	N.S.
FFA adequate control (< 800 μEq/L at 12 and 20 hr)	11	8	N.S.	4	4	N.S.
FFA inadequate control (> 800 μEq/L at 12 or 20 hr)	4	4		10	9	
FFA good control (> 50% fall at 4 hr and < 800 μEq/L at 12 and 20 hr)	6	4	N.S.	0	0	..
FFA poor control (< 50% fall at 4 hr or > 800 μEq/L at 12 or 20 hr)	9	8		14	13	
5-12 hr:						
Undifferentiated (i.e. whole group)	18	13	-	20	14	N.S.
FFA adequate control (< 800 μEq/L at 12 and 20 hr)	13	11	N.S.	3	2	N.S.
FFA inadeqaute control (> 800 μEq/L at 12 or 20 hr)	5	2		17	12	
FFA good control (> 50% fall at 4 hr and < 800 μEq/L at 12 and 20 hr)	10	9	N.S.	0	0	..
FFA poor control (< 50% fall at 4 hr or > 800 μEq/L at 12 or 20 hr)	8	4		20	14	

Table 9.
Number of patients with All R/T of S/V Type of V.P.B.

Start of treatment	NAA			Placebo		
	Total No.	No. with R/T S/V	Significance	Total No.	No. with R/T S/V	Significance
Pre 5 hr:						
Undifferentiated (i.e. whole group)	15	9	-	14	5	N.S.
FFA adequate control (< 800 μEq/L at 12 and 20 hr)	11	6	N.S.	4	2	N.S.
FFA inadequate control (> 800 μEq/L at 12 or 20 hr)	4	3		10	3	
FFA good control (> 50% fall at 4 hr and < 800 μEq/L at 12 and 20 hr)	6	2	N.S.	0	0	..
FFA poor control (< 50% fall at 4 hr or > 800 μEq/L at 12 or 20 hr)	9	7		14	6	..
5-12 hr:						
Undifferentiated (i.e. whole group)	18	9	-	20	9	N.S.
FFA adequate control (< 800 μEq/L at 12 and 20 hr)	13	7	N.S.	3	2	N.S.
FFA inadeqaute control (> 800 μEq/L at 12 or 20 hr)	5	2		17	7	
FFA good control (> 50% fall at 4 hr and < 800 μEq/L at 12 and 20 hr)	10	7	N.S.	0	0	..
FFA poor control (< 50% fall at 4 hr or > 800 μEq/L at 12 or 20 hr)	8	2		20	9	..

Table 10.
Number of patients with all R/T of V/V Type of V.P.B. related to degree of control of Plasma-F.F.A. in patients with Myocardial Infarction treated with N.A.A. or placebo.

Start of treatment	NAA			Placebo		
	Total No.	No. with R/T V/V	Significance	Total No.	No. with R/T V/V	Significance
Pre 5 hr:						
Undifferentiated (i.e. whole group)	15	11	-	14	12	N.S.
FFA adequate control (< 800 μEq/L at 12 and 20 hr)	11	7	N.S.	4	4	N.S.
FFA inadequate control (> 800 μEq/L at 12 or 20 hr)	4	4		10	8	
FFA good control (> 50% fall at 4 hr and < 800 μEq/L at 12 and 20 hr)	6	3	N.S.	0	0	..
FFA poor control (< 50% fall at 4 hr or > 800 μEq/L at 12 or 20 hr)	9	8		14	12	
5-12 hr:						
Undifferentiated (i.e. whole group)	18	12	-	20	11	N.S.
FFA adequate control (< 800 μEq/L at 12 and 20 hr)	13	11	N.S.	3	1	N.S.
FFA inadeqaute control (> 800 μEq/L at 12 or 20 hr)	5	2		17	10	
FFA good control (> 50% fall at 4 hr and < 800 μEq/L at 12 and 20 hr)	10	9	p=0·032	0	0	..
FFA poor control (< 50% fall at 4 hr or > 800 μEq/L at 12 or 20 hr)	8	3		20	11	..

Table 11.
Number of patients with all R/A Type of V.P.B. related to degree of control of Plasma-F.F.A. in patients with Myocardial Infarction treated with N.A.A. or placebo.

Start of treatment	NAA			Placebo		
	Total No.	No. with R/A	Significance	Total No.	No. with R/A	Significance
Pre 5 hr: Undifferentiated (i.e. whole group)	15	4	-	14	10	p=0·02
FFA adequate control (< 800 μEq/L at 12 and 20 hr)	11	3	N.S.	4	3	N.S.
FFA inadequate control (> 800 μEq/L at 12 or 20 hr)	4	1		10	6	
FFA good control (> 50% fall at 4 hr and < 800 μEq/L at 12 and 20 hr)	6	1	N.S.	0	0	..
FFA poor control (< 50% fall at 4 hr or > 800 μEq/L at 12 or 20 hr)	9	3		14	10	
5-12 hr: Undifferentiated (i.e. whole group)	18	7	-	20	5	N.S.
FFA adequate control (< 800 μEq/L at 12 and 20 hr)	13	6	N.S.	3	1	N.S.
FFA inadeqaute control (> 800 μEq/L at 12 or 20 hr)	5	1		17	4	
FFA good control (> 50% fall at 4 hr and < 800 μEq/L at 12 and 20 hr)	10	5	N.S.	0	0	..
FFA poor control (< 50% fall at 4 hr or > 800 μEq/L at 12 or 20 hr)	8	2		20	10	..

Table 12.
Number of patients with any R/A of V/V Type related to degree of control of Plasma-F.F.A. in patients with Myocardial Infarction treated with N.A.A. or placebo.

Start of treatment	NAA			Placebo		
	Total No.	No. with R/A V/V	Significance	Total No.	No. with R/A V/V	Significance
Pre 5 hr:	15	2	-	14	8	p=0·02
Undifferentiated (i.e. whole group)						
FFA adequate control (< 800 μEq/L at 12 and 20 hr)	11	2	N.S.	4	3	N.S.
FFA inadequate control (> 800 μEq/L at 12 or 20 hr)	4	0		10	5	
FFA good control (> 50% fall at 4 hr and < 800 μEq/L at 12 and 20 hr)	6	0	N.S.	0	0	..
FFA poor control (< 50% fall at 4 hr or > 800 μEq/L at 12 or 20 hr)	9	2		14	8	
5-12 hr:	18	6	-	20	3	N.S.
Undifferentiated (i.e. whole group)						
FFA adequate control (< 800 μEq/L at 12 and 20 hr)	13	6	N.S.	3	1	N.S.
FFA inadeqaute control (> 800 μEq/L at 12 or 20 hr)	5	0		17	2	
FFA good control (> 50% fall at 4 hr and < 800 μEq/L at 12 and 20 hr)	10	5	N.S.	0	0	..
FFA poor control (< 50% fall at 4 hr or > 800 μEq/L at 12 or 20 hr)	8	1		20	3	..

Table 13.
Number of patients with any R/A of S/V Type related to degree of control of Plasma-F.F.A. in patients with Myocardial Infarction treated with N.A.A. or placebo.

Start of treatment	NAA			Placebo		
	Total No.	No. with R/A S/V	Significance	Total No.	No. with R/A S/V	Significance
Pre 5 hr: Undifferentiated (i.e. whole group)	15	4	-	14	4	N.S.
FFA adequate control (< 800 μEq/L at 12 and 20 hr)	11	3	N.S.	4	2	N.S.
FFA inadequate control (> 800 μEq/L at 12 or 20 hr)	4	1		10	2	
FFA good control (> 50% fall at 4 hr and < 800 μEq/L at 12 and 20 hr)	6	1	N.S.	0	0	..
FFA poor control (< 50% fall at 4 hr or > 800 μEq/L at 12 or 20 hr)	9	3		14	4	
5-12 hr: Undifferentiated (i.e. whole group)	18	4	-	20	4	N.S.
FFA adequate control (< 800 μEq/L at 12 and 20 hr)	13	3	N.S.	3	1	N.S.
FFA inadeqaute control (> 800 μEq/L at 12 or 20 hr)	5	1		17	3	
FFA good control (> 50% fall at 4 hr and < 800 μEq/L at 12 and 20 hr)	10	2	N.S.	0	0	..
FFA poor control (< 50% fall at 4 hr or > 800 μEq/L at 12 or 20 hr)	8	2		20	20	

Death

One patient in the N.A.A. treated group died. Death occurred 10 hours after starting treatment, which was commenced 7 hours from onset of symptoms. The plasma F.F.A. concentration in this patient was 1880 μEq/L at the start of the study, and had fallen to 970 μEq/L by 4 hours. No further estimates were made before death because of the insertion of a cardiac pacemaker and multiple therapeutic interventions.

Necropsy showed ventricular rupture.

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Serum Creatine Kinase Measurements

There was no significant difference in serum C.K. concentrations between the N.A.A. and placebo treated groups (Figure 15), and no significant difference in the concentrations of C.K between the subgroups with F.F.A. good or poor, adequate or inadequate control in either the pre or post 5-hour patients treated with N.A.A.

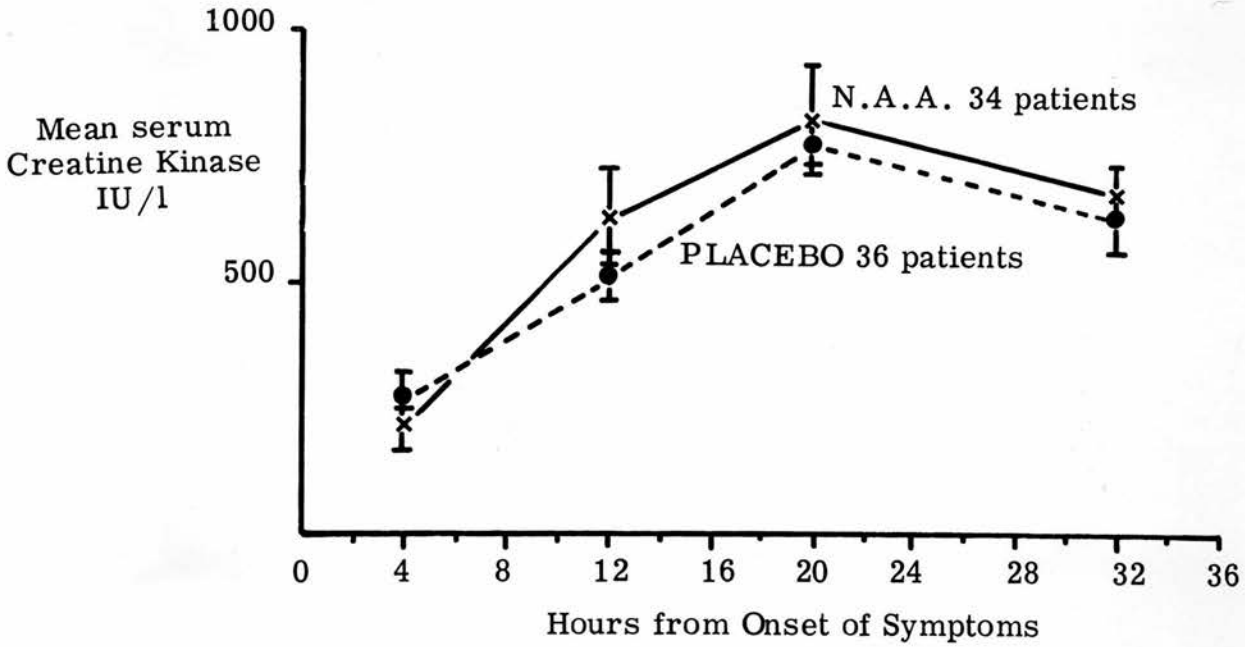

Figure 15. Serum Creatine Kinase in Patients treated with N.A.A. or Placebo within 12 Hours of the Onset of Myocardial Infarction.

Plasma Total Catecholamines Measurements.

In every case the first sample showed a concentration greater than the normal range. Throughout the study period no sample showed a value in the normal range, including, therefore, the 2 patients seen within 2 hours of the onset of symptoms and the patient not seen until 11.25 hours had elapsed.

The mean curve for the whole group, with the values related to the time of onset of symptoms (Figure 16) shows that the mean total plasma catecholamines concentration was consistently elevated throughout the study period to approximately twice normal levels. The relationship between mean plasma total catecholamines and the incidence of ventricular tachycardia and R/T, and R/apex T V.P.B. in both N.A.A. and placebo treated groups was examined. There is no significant increase in the incidence of the arrhythmias with increasing mean plasma catecholamine concentrations or with peak plasma catecholamine concentrations (See Appendix A).

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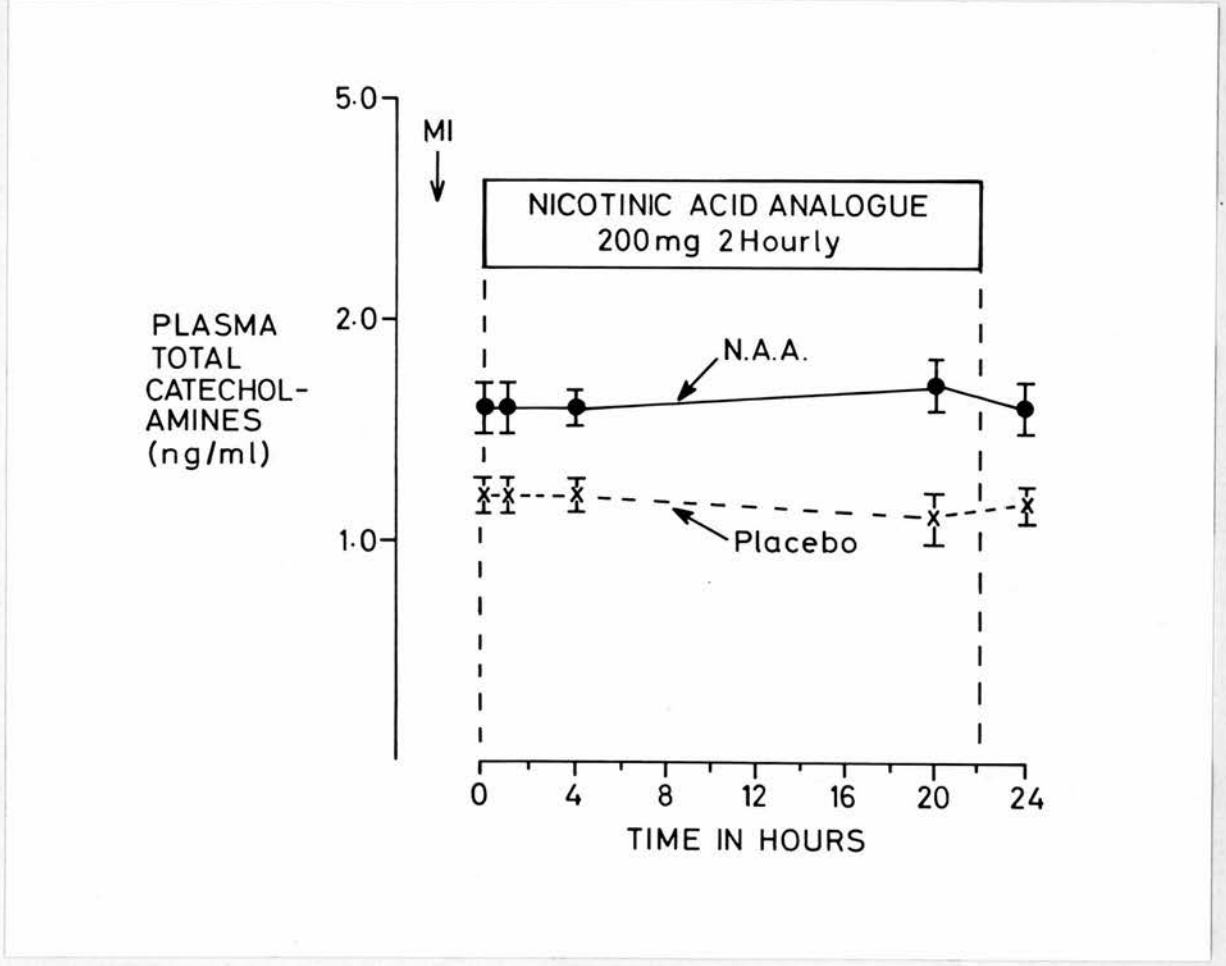

Figure 16. Plasma Total Catecholamines in Patients with Myocardial Infarction Treated with N.A.A. or Placebo. (Differences between each concentration = N.S.).

Blood Glucose Measurements

There was no significant difference in blood glucose concentrations between the N.A.A. and placebo groups on entry into the study, nor between the previously described subgroups during the treatment period. (Table 14).
(Due to blood clots in some specimens and a problem with quality control of the blood glucose method,results were not obtained on all specimens submitted for analysis. Where there are deficiencies, the number of patients contributing to each group is, therefore, given in Table 14.)

The subgroups shown are those treated with N.A.A. within 5 hours of the onset of symptoms.

	Admission	On Treatment With N.A.A.	Off Treatment With N.A.A.	Follow-up Period
NAA Whole group (34)	87.6 ±4.2	91.2 ±4.2 (30)	92.3 ±9.6 (31)	84.9 ±7.7
Placebo Whole group (36)	89.4 ±4.3	94.3 ±9.2	81.9 ±6.4	77.9 ±3.2
Difference	NS	NS	NS	NS
F.F.A. Good Control group	96.3 ±17.3	96.5 (2)	88.0 ±12.4 (3)	66.5 ±5.6
F.F.A. Poor Control group	91.9 ±6.9	87.6 ±8.9	111.6 ±25.4	119.6 ±26.8
Difference	NS	-	NS	NS

(mg/% Mean ± S.E.M)

Table 14

Blood Glucose measurements in Patients with Acute Myocardial Infarction

( ) = No. of Patients in Group.

Plasma Triglyceride Measurements.

There were significantly higher plasma concentrations in the placebo group than in the N.A.A. group on entry into the study, but this elevation did not persist into the treatment period. During therapy there was no significant difference between the groups and no change in plasma triglyceride concentrations attributable to treatment with N.A.A.

Plasma Concentration of N.A.A.

Plasma 5-fluoronicotinic acid (5-F.N.A.), the main metabolite of N.A.A. was measured in all patients. The mean plasma concentrations were significantly lower 4 hours after starting treatment in the subgroups with poor control of F.F.A., and during the subsequent 20 hours, when compared with those concentrations occurring in the subgroup with good control ($p = 0.025$). (Figure 17). It was clear from the individual curves that a steadily rising plasma concentration of 5-F.N.A. was necessary to maintain F.F.A. control. Where concentrations of 5-F.N.A. fluctuated, or failed to increase with time, the control of F.F.A. was poor. These patterns suggest tachyphylaxis

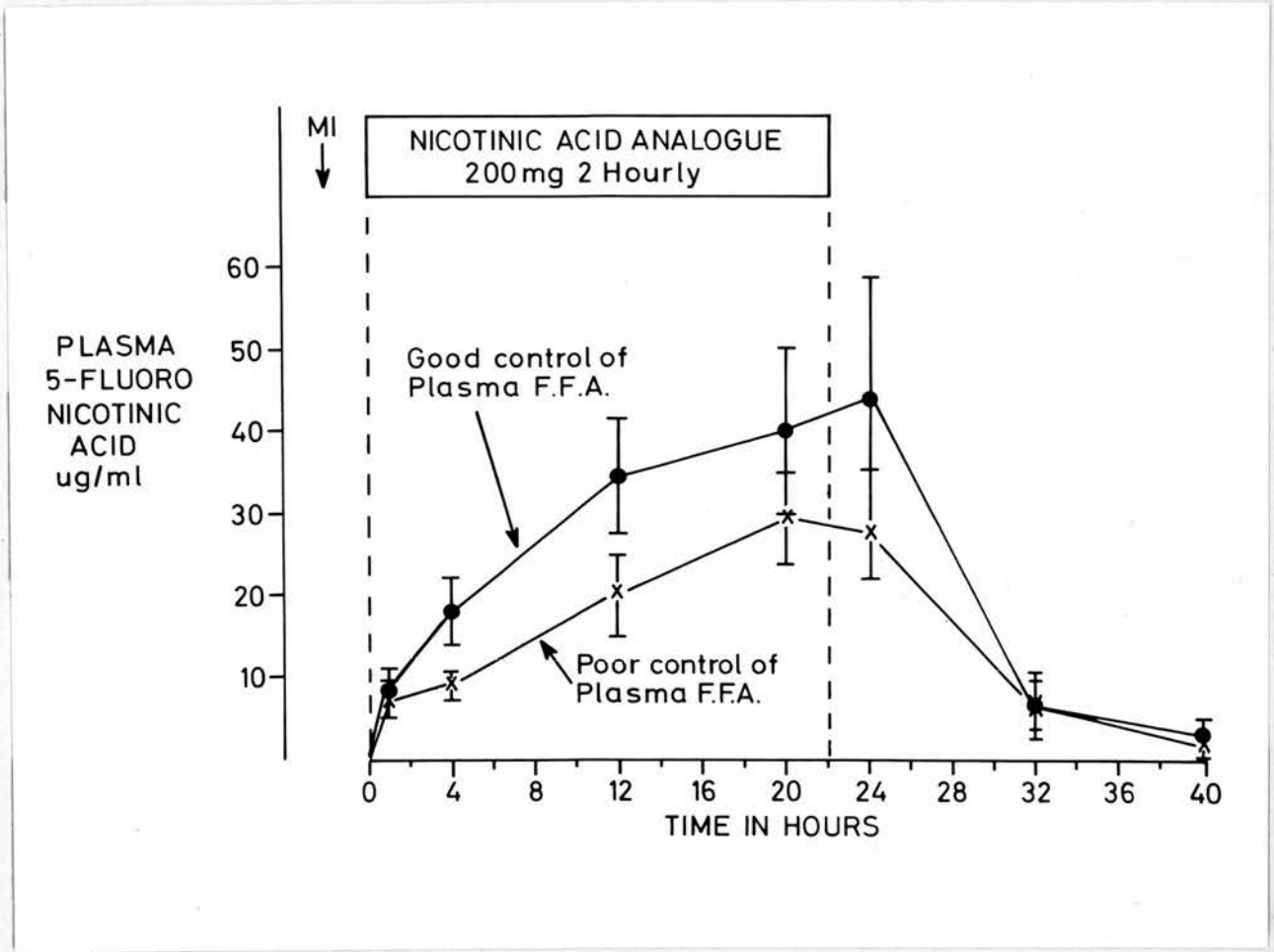

Figure 17. Plasma 5 - Fluoronicotinic Acid levels in Patients with Myocardial Infarction Treated with N.A.A.

Side-Effects of N.A.A.

In five of the 34 patients given N.A.A. there was mild facial skin flushing. More patients vomited in the group given N.A.A. within 5 hours of the onset of symptoms than in the same group of placebo patients (p= 0.05) Vomiting occurred later in the group treated with N.A.A. The mean time of onset of vomiting was 18.2 hours after starting N.A.A. and 5.7 hours after starting placebo (p= 0.005) In the N.A.A. subgroups, vomiting started at a mean time of 17 hours in those with good control and at a mean time of 7.8 hours in those with poor control (p= 0.003).

Morphine Requirements of Patients in Trial.

Table 15 shows the distribution by treatment group of patients requiring morphine in doses from 10 - 30 mgm or more and those who were not given morphine either by the G.P. or in the C.C.U.

There was no difference between the whole groups in terms of the severity of pain as judged by the morphine requirements. In particular there is no significant difference in the numbers with very mild pain requiring little or no analgesic, or in the numbers requiring the higher doses for severe pain. The mean dose of morphine given to the N.A.A. group was 26.2 mgm, and that given to the placebo group was 20.20 mgm. The difference is not significant. (p = N.S.) Table 15 also shows the same assessment of morphine requirements for the pre-5 hours subgroups. (Good control = 50 % fall in F.F.A. and F.F.A. in normal range at 12 and 20 hours).

Again there are no significant differences between the groups. The mean dose of morphine for the good control group was 24.1 mgm, and that for the poor control group was 26.5 mgm.

This information supports the view that the excess of vomiting in the N.A.A. treated group was due to the N.A.A. rather than to any difference in the quantity of other drugs given which have major emetic side effects.

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Morphine Requirements of Whole Study Group

	0mg	⩽10mg	>10mg ⩽20mg	>20mg ⩽30mg	>30mg	Total
'.A.A.	7	8	4	10	5	34
'lacebo	6	11	11	4	8	36

Morphine Requirements of Pre-5 hours N.A.A. Treated Subgroups

	0mg	⩽10mg	>10mg ⩽20mg	>20mg ⩽30mg	>30mg	Total
ood Control Subgroup	0	3	0	1	2	6
oor Control Subgroup	2	0	0	6	2	10

Table 15

Morphine requirements of Patients with Myocardial Infarction given N.A.A.

Blood Pressure Recordings

The blood pressure was recorded by sphygmomanometer cuff before treatment commenced, and 4 hourly during treatment. (See Table 16) Before treatment commenced the mean systolic and diastolic blood pressures were significantly lower in the N.A.A. group compared with the placebo group. During treatment however, the pressure in the N.A.A. group rose towards that in the placebo group and the mean minimum systolic and diastolic pressures were not significantly different. The mean maximum pressures in the N.A.A. treated group, although rising during the treatment period, never equalled the readings in the placebo group. The N.A.A. did not therefore produce hypotension, nor did it hold the pressure in the N.A.A. group at a significantly lower level than that in the placebo group. It may, however, have prevented the peak pressures in the N.A.A. group reaching those of the placebo group, although this is speculative in the light of the lower starting pressures in the N.A.A. group.

	Before Treatment		During Treatment			
	Mean Systolic B.P.	Mean Diastolic B, P.	Maximum Systolic B.P.	Minimum Systolic B.P.	Maximum Diastolic B.P.	Minimum Diastolic B.P.
NAA (34)	121 ±7.6	73 ±2.7	135 ±5.4	97 ±4.6	83 ±2.2	57 ±2.7
Placebo (36)	145 ±4.7	85 ±3.0	148 ±4.2	99 ±2.7	95 ±2.3	57 ±2.5
P =	<0.05	<0.05	<0.05	N.S.	<0.05	N.S.

Table 16

Blood Pressure recordings (Mean ± S.E.M.) before & during Treatment with NAA & Placebo in patients with Acute Myocardial Infarction.

Discussion.

Sudden death within the first few hours of the onset of symptoms associated with acute myocardial infarction accounts for the major part of the mortality from coronary heart disease. The actual mechanism of sudden death is not certain but, based on experience in coronary care units and in mobile intensive care units, it seems to be due to disturbances of cardiac rhythm, in particular ventricular fibrillation. Arrhythmias occur principally in response to inadequate blood flow in a coronary artery with consequent primary, or direct, disruption of normal and fundamental metabolic mechanisms in the myocardium.

There is a major systemic hormonal response associated with the onset of symptoms of the acute event, with consequent changes in plasma concentration of usual myocardial metabolites. The presentation of abnormal patterns of essential metabolites to the already embarrassed myocardium represents a secondary, or indirect, disruption of normal processes.

From experimental studies it appears that in the acutely ischaemic myocardium there is patchy reduction in perfusion and hence oxygenation, probably with a constantly changing distribution of hypoxic and underperfused areas. In an underperfused area, F.F.A. utilisation is reduced with a consequent rise in the local concentration. This inhibits the utilisation of glucose and glycogen which are released from tissue stores in response to hypoxia. In other areas key enzyme systems cease to function due to total anoxia and, therefore, essential ionic transport systems fail. Local accumulation of fatty acyl CoA esters inhibit the enzyme transport mechanisms for A.T.P. at inner mitochondrial

membrane level and hence further endanger normal cell membrane function.

The systemic release of catecholamines raises plasma F.F.A. concentrations by stimulation of adipose tissue lipolysis and the consequent increased uptake of F.F.A. by the myocardium may further augment the local changes which have already occurred. The local release of myocardial catecholamines may have a direct effect on the myocardial cell membrane and decrease its stability so encouraging spontaneous pacemaker activity. The contribution of the systemic increase in catecholamine activity to such an effect is undetermined.

There is abnormal glucose tolerance after myocardial infarction, and increased glucagon secretion contributes to a rise in blood glucose. Rises in plasma cortisol and growth hormone output may contribute to insulin suppression and hence altered tissue uptake of glucose.

The combined effects of high catecholamines, high F.F.A. and reduced availability of glucose produce, therefore, local areas of fluctuating efficiency in the maintenance of ionic pumps and of stable impulse formation, conduction and perpetuation. The end result is reduction in mechanical performance, and the appearance of ventricular arrhythmias. It is not yet possible to define which, if any of the abnormal factors is the sole or even a prime cause of the extreme electrical instability which preceeds the onset of ventricular fibrillation.

One of the areas of major uncertainty is the interrelationship of these profound biochemical changes with the known electrophysiological events,but there is current speculation that the relative availability of F.F.A., glucose and the inorganic ions may be of great importance in the genesis of V.F.

The hypothesis that F.F.A. not only contribute to the adverse metabolic balance in the hypoxic myocardium but are a major factor in cell membrane dysfunction, has been proposed by Oliver and his co-workers. The therapeutic implication of their observation is

important as the reduction of high intracellular F.F.A. concentrations would not only diminish any direct effects they might have on enzyme systems and the membranes, but would also reduce their inhibitory effect on the uptake of glucose. This could produce a favourable balance of substrates available to the myocardium during hypoxic conditions.

The mechanism by which F.F.A. have a direct toxic effect on the cell membrane was ascribed by Oliver to a non specific detergent effect of F.F.A. soaps produced by F.F.A. combining with Acyl CoA and calcium and magesium ions. More recently, however, Shug and Shrago have confirmed the presence of Fatty Acyl CoA esters in the mitochondria, and they also demonstrated a specific inhibitory effect of these esters on the enzyme systems essential for the transport of A.T.P. across the inner mitochondrial membrane. If the intracellular concentration of F.F.A. could be reduced, therefore, during the phase of acute hypoxia, A.T.P. might be made more readily available, membrane function might be improved, the extent of the infarction restricted, and the incidence of clinically detectable arrhythmias reduced.

The Oliver hypothesis specifically relates high plasma F.F.A. concentrations to the incidence of ventricular arrhythmias. The investigations described in the foregoing work were specifically designed to test this hypothesis in its clinical aspect, by showing firstly that plasma F.F.A. concentrations could be lowered in the acute situation in man, and secondly by observing the effects of this manoeuvre on the incidence of ventricular arrhythmias. Of particular importance were observations on the incidence of those arrhythmias previously reported to have predictive value for the onset of ventricular fibrillation.

The initial studies demonstrated that plasma F.F.A. concentrations could be lowered in man with A.M.I. without haemodynamic effects which might influence myocardial perfusion, and that suppression of lipolysis could be achieved in the face of the persistent catecholamine release which occurs in the acute stress conditions accompanying

accompanying myocardial infarction. There was no detected side effect attributable to the lowering of plasma F.F.A., although late onset nausea and vomiting occurred which was attributed to a direct gastic irritant effect of the N.A.A. used to inhibit lipolysis. There was no evidence of a consistent effect of the N.A.A. on blood sugar concentrations which might have independently altered the balance of substrates presented to the myocardium. Nor was there any effect on plasma total catecholamines.

In the double blind controlled study in 81 patients with A.M.I., antilipolytic treatment with the N.A.A. reduced elevated plasma F.F.A. concentrations to normal levels, but the experience of the pilot studies was not thereafter confirmed, in that the antilipolytic regimen used was not wholly satisfactory. Only half of the patients treated early had consistent control of plasma F.F.A., and variations in the speed of absorption of the oral preparation of N.A.A. during the first few hours of acute infarction may account for this. The excess vomiting attributable to the N.A.A. may have led to the later variability in F.F.A. control. The analogue had to be administered every 2 hours to maintain the plasma F.F.A. lowering effect and this may account for gastric irritation, nausea and vomiting in some patients, as the N.A.A. is presented as a strongly acid salt and the total dose is released rapidly on contact of the capsule with gastric contents.

The rise in plasma concentrations of the metabolite, 5-fluoronicotinic acid, required to maintain F.F.A. control indicates tachyphylaxis, although this may not necessarily matter if after rapid initial control,F.F.A. need only be consistently lowered for a relatively short period of 12-24 hours. The rebound of plasma F.F.A. levels after withdrawal of the N.A.A. was not associated with any adverse effects. It might be unwise, however, to suppress elevated plasma F.F.A. levels for a period shorter than 24 hours, since an earlier rebound

rebound would present high plasma F.F.A. concentrations to the myocardium at a more critical phase of ischaemia.

The changes produced by N.A.A. in plasma concentrations of F.F.A. were not associated with a reduction in the plasma total catecholamines. These remained at twice normal levels in all patients for atleast 48 hours from the onset of symptoms, and no relationship between mean or peak plasma total catecholamine concentrations and ventricular arrhythmias could be demonstrated. (See Appendix A)

The clearly independent lowering of plasma F.F.A. did appear to be related to the incidence of ventricular arrhythmias, and in assessing the success of prevention of any of the ventricular arrhythmias, it is stressed that the criterion used for success was that any given patient should have no episodes of that arrhythmia during the recording period of 48 hours and not just that there should be a reduction in the number of arrhythmic events. Furthermore, the effect of F.F.A. suppression was considered on each individual type of arrhythmia rather than on an undefined group of events which might have differing origins and a differing natural incidence in various parts of the recording period. The result of this detailed assessment was that where N.A.A. was given during the first 5 hours after the onset of symptoms there were fewer patients with ventricular tachycardia, and this was related to the degree of suppression of F.F.A. Where there was a 'good' control no patient had V.T. and there were no episodes of V.T. with coupling intervals of <400 msecs. Furthermore, such V.T. as did occur in the N.A.A. treated patients with less than satisfactory control of F.F.A. was in the earlier hours after starting treatment i.e. when F.F.A. were coming under control but had not long been consistently in the normal range. This is reflected in the significantly earlier mean time of onset of V.T. in the group treated within 5 hours of the onset of symptoms.

N.A.A. appeared to have no effect on the number of beats in the runs of V.T. but there was a strong trend towards a reduction in the incidence of V.T. including coupling intervals of <400msecs. in the N.A.A. groups treated within 5 hours. This trend does not

not reach statistical significance but is in keeping with a general reduction in the incidence of V.T., and R/T phenomena with short coupling intervals.

There was also a significant reduction in the number of patients with all types of R upon apex T.V.P.B. and in particular in the number with V.P.B. in which the R wave interrupted the apex of the T wave of a preceding V.P.B.; this latter group being that said to predict most reliably the subsequent onset of ventricular fibrillation.

A criticism of this interpretation of the results of the double blind study is that the reductions in the incidence of the ventricular arrhythmias were identified by retrospective analysis of the total data from the study. The 0 - 12 hours randomisation period chosen initially was based on earlier published reports of the natural history of ventricular arrhythmias, The rapid natural decrease in the incidence of ventricular tachycardia, and to a less extent of V.P.B., in the first 12 hours after the onset of symptoms was only revealed after study of the control group of this trial and led to the retrospective appraisal of the total study group. Inevitably therefore the design of this study did not include the facility for random allocation of patients to treatment groups at hourly intervals of time from the onset of symptoms. During the course of this study the results of independent studies using serial sampling of blood in the first hours of the illness became available. These studies revealed more rapid rates of change in the metabolic indices than previously observed and also that the onset of major metabolic disturbances was earlier than previously believed. The peak elevation of plasma F.F.A. was previously thought to occur at 8 hours from the onset of symptoms, but Vetter et al, demonstrated that it occurs at 2 hours or less from the onset of symptoms. It might therefore be expected that if a beneficial effect were to be obtained from lowering plasma F.F.A. concentrations it would be most obvious in those patients treated during that period. Treatment initiated at a later stage after the onset of symptoms might be less/

less effective if the acutely ischaemic myocardium had already been exposed to high levels of F.F.A. for some time. The positive findings obtained in this study by the retrospective division of data on a 0-5 hours and 5-12 hours basis is in keeping with these expectations. Retrospective sub division of the data by hourly intervals before 5 hours resulted in such small numbers in each hourly group that formal statistical analysis was not possible and subdivisions of the study data beyond 5 hours from the onset of symptoms did not show significant differences between the N.A.A. and placebo treated groups.

A further criticism of the study is again related to the 12 hour randomisation period and the subsequent division of the data. The difference in the mean time of admission to the trial of those treated within 5 hours of the onset of symptoms might have accounted for an increase in early serious ventricular arrythmias in the placebo groups and a bias in favour of the N.A.A. treated group. A converse bias might have operated in the 5-12 hour group. This cannot however, affect the differences observed in the patient incidence of ventricular tachycardia in relation to the degree of F.F.A. control achieved within the N.A.A. group, since there was no difference in the mean time of admission to the trial between the N.A.A. treated subgroups based on the pattern of F.F.A. control.

The group with lowered plasma F.F.A. did not have lower plasma creatine kinase levels. This might be interpreted as suggesting that lowering of plasma .F.F.A. did not restrict the size of the infarction as might be expected from experimental work. The number of C.K. estimations done was insufficient to allow formal comparison of areas below the C.K. curve (Sobel et. al. 1973) as the initial aim of C.K. measurements in this study was to show only that there was no gross difference in the initial size of infarction which could bias either group.

The extent of the unstable peri-infarction ischaemic area could nevertheless have been minimised, and recent studies have demonstrated that the sum of the ST segment elevations on the surface of the myocardium is reduced where antilipolytic therapy is given in animal experiments. Clearly, therefore, specific studies of antilipolytic therapy in man with AMI should be undertaken when currently evolving methods of measuring infarct size in man have been further developed.

The possibility of adverse effects of antilipolytic therapy is raised by the higher incidence of some ventricular arrhythmias observed in some subgroups treated with N.A.A. between 5 and 12 hours after the onset of symptoms. The incidence of the arrhythmias does not increase in the group given N.A.A. but it fails to fall in the manner expected if the N.A.A. were ineffective and the pattern in the placebo group was followed. The excess vomiting which occurred in the N.A.A. group did so at this time, and may have prevented the gradual disappearance of the remaining arrhythmias.

The site of action of the N.A.A. is not elucidated by this study. The antilipolytic effect is probably on the peripheral tissues, and any beneficial effects would be achieved by lowering circulating F.F.A. and hence the amount presented for uptake by the myocardium.
That there may be a local effect of N.A.A. on the myocardium is suggested by the lack of relationship between plasma F.F.A. and the incidence of arrhythmias in the pre 5 hours placebo subgroups with plasma F.F.A. equivalent to "adequate control" in the treated groups. The effects of N.A.A. could be due, therefore, to local inhibition of lipolysis or to a primary antiarrhythmic effect of the drug unrelated to the effect of the N.A.A. on plasma F.F.A. concentrations. These questions remain unresolved.

The findings described in this thesis support the view that the high plasma F.F.A. concentrations observed in man with acute myocardial infarction represent one of the factors in the genesis of ventricular arrhythmias in the ischaemic myocardium in man. The principal implication of this work is that lowering plasma F.F.A. concentrations in the earliest stages of the illness will lower the incidence of some of these arrhythmias. Any possible reduction in the incidence of/

of ventricular fibrillation as a consequence of this action remains purely speculative, as consideration of the placebo group studies indicated that whilst ventricular arrhythmias represent disturbed myocardial function, they occur too frequently to have firm predictive value for ventricular fibrillation in the individual patient. Nevertheless the improvement in the balance of metabolites presented to the myocardium achieved by lowering the plasma F.F.A. does seem to be reflected in a decrease in the incidence of ventricular arrhythmias. It should thereby contribute to the reversal of the adverse conditions at cell membrane level which would, if uncorrected, allow the appearance of ventricular fibrillation.

The maximum possible effect of antilipolytic therapy may not have been realised by the studies described in this thesis, due to the variable success of F.F.A. control and the limited numbers of patients studied very early in the course of AMI to the extent that a statement about the effect on the incidence of ventricular fibrillation could not be made.

If all the metabolic abnormalities described in the situation of AMI contribute to cell membrane instability then correction of any one may produce an advantageous effect. β-blockade of the excess catecholamine secretion reduces the incidence of arrhythmias but does so at the expense of the desirable inotropic activity of the catecholamines, and the risk of precipitating ventricular failure is increased. Glucose Potassium and Insulin infusions are also a logical approach to supporting the myocardium. Glucose-insulin infusions may not only stimulate myocardial carbohydrate metabolism but will also reduce the availability of F.F.A. by the stimulation of F.F.A. esterification and the inhibition of lipolysis. The infusion of large volumes of fluid at the earliest stage of the illness is, however, impracticable and may be haemodynamically undesirable. Attempts to use this mode of therapy have not so far produced definite evidence of a beneficial effect. Infusion of glucose insulin and potassium aimed specifically at lowering plasma F.F.A. to a concentration below the established myocardial F.F.A. uptake threshold, appears, however, to have been associated with a reduced mortality. (Rogers, et. al. 1976)

SUMMARY

The purpose of this thesis was four fold: the relevance of ventricular arrhythmias to the risk of sudden death during A.M.I. has been considered by review of the literature, and the high incidence of ventricular arrhythmias without subsequent ventricular fibrillation in patients with uncomplicated A.M.I. has been emphasized in the original work that is presented. The relationship between these arrhythmias and ventricular fibrillation has been discussed and it has been shown to be less clear cut than previous opinions have maintained.

The hypothesis that F.F.A. may be toxic when presented to the ischaemic myocardium has been examined, and the experimental and clinical evidence relevant to this hypothesis discussed.

A method of safely lowering elevated plasma F.F.A. in man with A.M.I. has been developed and it has been applied as a test of the hypothesis under discussion. The possible beneficial effects of antilipolytic therapy have been suggested by a probable reduction in the incidence of ventricular arrhythmias and the findings are supported by work from other sources published since the studies were completed. The short comings and advantages of this mode of treatment have been discussed with respect to the early management of patients with acute myocardial infarction.

The Relevance of the Thesis to Past, Present and Future Work.

The initial observations of the relationship between raised plasma F.F.A. and ventricular arrhythmias passed through the well known stages of confirmation and rebuttal but, nevertheless, survived to form the basis of the established hypothesis that F.F.A. can cause ventricular arrhythmias. The hypothesis was tested in animal models and supportive evidence found. It remained to return to the clinical arena and test the hypothesis in man with acute myocardial infarction. This thesis reports the only known attempt at this manoeuvre and is the rational development from the earlier work. The parallel work on the effect of F.F.A. on the size of the infarction has received encouragement from the work of this thesis and the impressive results obtained in reduction of the area of ischaemic damage in animal models, will surely lead to the exploration in man of factors which will limit infarct size.

The observation in this thesis, that any beneficial effect of antilipolytic treatment is dependent upon its being given in the earliest hours after the onset of symptoms associated with infarction, gives clear guidlines about the design of future studies. These will apply not only to further tests of the F.F.A. hypothesis but to all attempts at prevention or minimisation of the complications of acute myocardial infarction.

This work also supports the view that intense enquiry should continue into the predictive value of multiple risk factors in indentifying the individual most at risk of developing ventricular fibrillation. It is clear that present static coronary care units and mobile intensive care teams can make a valuable, but limited, impression on mortality. Thus the search for a self administered therapy which, if taken at the onset of symptoms, will prevent, restrict or at least postpone the complications of an episode of ischaemia must continue. The suggestion made in this thesis that an orally administered antilipolytic therapy may not only prevent arrhythmic complications, but may do so by favourably altering myocardial/

myocardial metabolism, such that myocardium of doubtful viability may also be salvaged, is a step in that direction.

Glucose, insulin and potassium therapy, β-blockade and antilipolytic therapy could all be reassessed at hourly intervals from the onset of symptoms. Computer monitoring and analysis could be utilised to detect changing patterns of arrhythmias and used along with the newer methods of estimating infarct size to further evaluate the modes of therapy described.

The natural history of each of the ventricular arrhythmias is still obscure, as is their relationship with ventricular fibrillation The natural pattern of decline in incidence of each arrhythmia may differ for each type, and the rate of change in incidence should clearly be taken into account in future studies. The scale of studies needed to prove that prevention of ventricular fibrillation by any of the suggested methods is possible is probably beyond the scope of current research funds and facilities in this country.

Prevention of the whole syndrome of coronary disease must remain the prime aim, but recent trends in the results of studies directed at the correction of some of the known risk factors mitigate against an early solution to the problem. In the meantime therefore, it is reasonable to pursue new areas of therapeutic support for the myocardium at the times when it seems to suffer, like the world at large, from an energy crisis.

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APPENDIX A

Plasma Total-catecholamine Measurements in Placebo treated Patients

Previous studies have related elevated levels of catecholamines in urine and blood to the severity of infarction and to the risk of developing ventricular arrhythmias. A relationship between raised plasma adrenaline concentrations and ventricular arrhythmias and between plasma nonadrenaline concentrations and the incidence of arrhythmias has also been reported.

These earlier studies did not provide a closely spaced sequence of measurements of plasma catecholamines or a concurrent continuous ECG recording for identification of ventricular arrhythmias.

The placebo group of the double blind trial reported in this thesis provides the opportunity to further consider the relationship in a group of patients with uncomplicated myocardial infarction.

In this placebo group of patients there was no relationship between the incidence of ventricular tachycardia, or R-on-T VPB of any type, and the mean or the maximum plasma total catecholamine concentrations in patients during the first 40 hours after AMI. (See fig. i and ii) Further there was no relationship between mean or peak catecholamine concentrations and the incidence of R-on-apex T of S/V type, or of the V/V type which has been said to be a precursor of ventricular fibrillation. In some instances the patients with the highest mean and peak plasma total catecholamine concentrations failed to show any episode of serious ventricular arrhythmias.

Mean plasma total catecholamine concentrations for the whole group did not fall significantly during the study and remained at approximately twice the upper limit of the reference range throughout the recording period (See Fig. 16). The overall incidence of each arrhythmia however, decreased rapidly with time and although still being observed at the end of the study the incidence had fallen markedly by 30 hours from the onset of symptoms. At this time the mean total-plasma-catecholamine concentrations were still at values recorded within the first hour after the onset of symptoms.

If excess levels of plasma catecholamines are a major cause of ventricular arrhythmias, such arrhythmias should be observed as long as the plasma catecholamine concentration levels remain elevated, and disappear as the catecholamine concentration eventually declines after the acute phase of the illness. This study demonstrated that the initial incidence of arrhythmias declines before there is any change in plasma total catecholamine concentrations and it therefore appears, that while high local concentrations of catecholamines may be involved with other influences to promote the initial development of arrhythmias, it is unlikely that the elevated plasma catecholamines can be the sole explanation of ventricular arrhythmias during acute ischaemia and infarction.

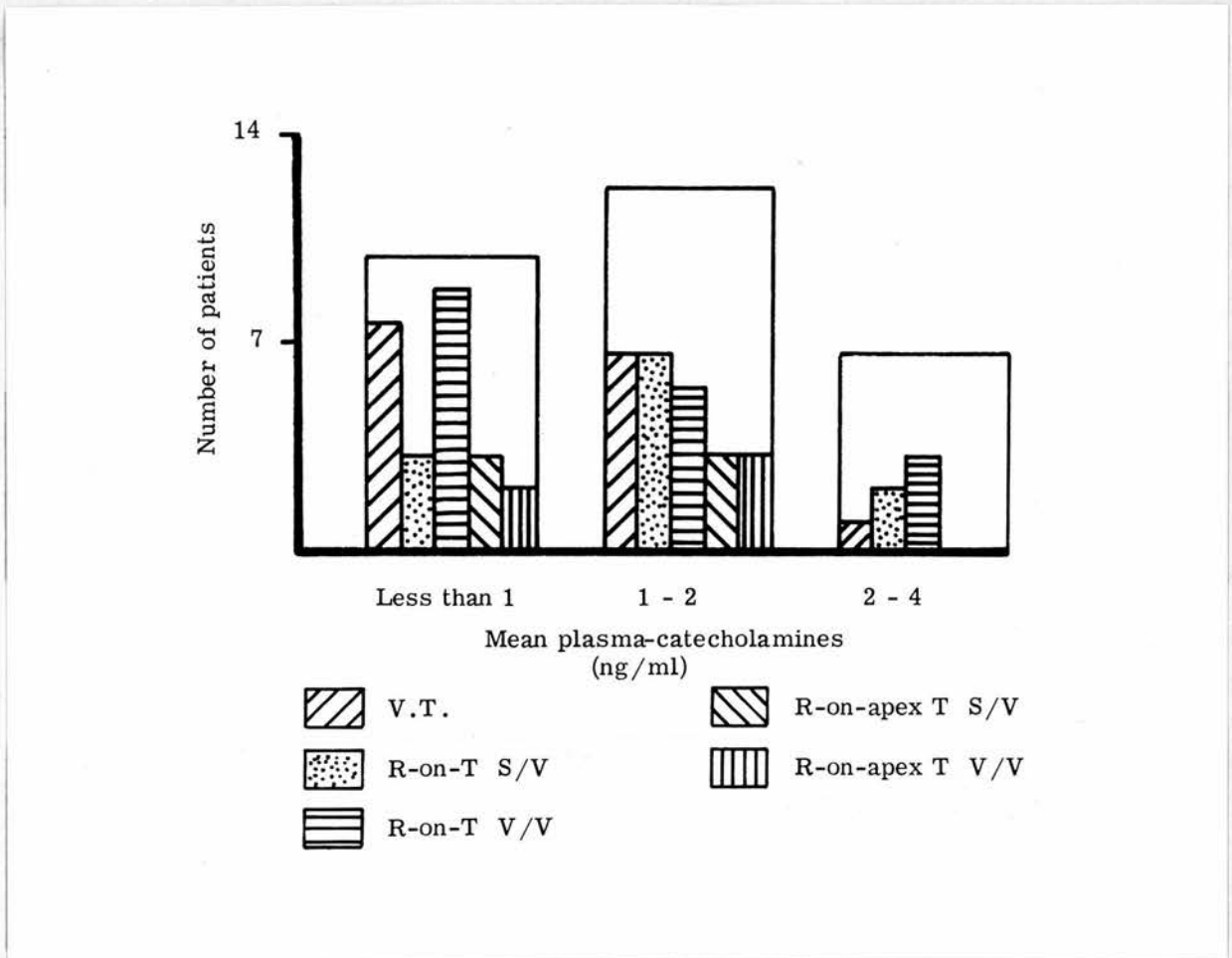

Figure i. Relationships between mean plasma-total-catecholamine concentrations (ng/ml) and ventricular arrhythmias.

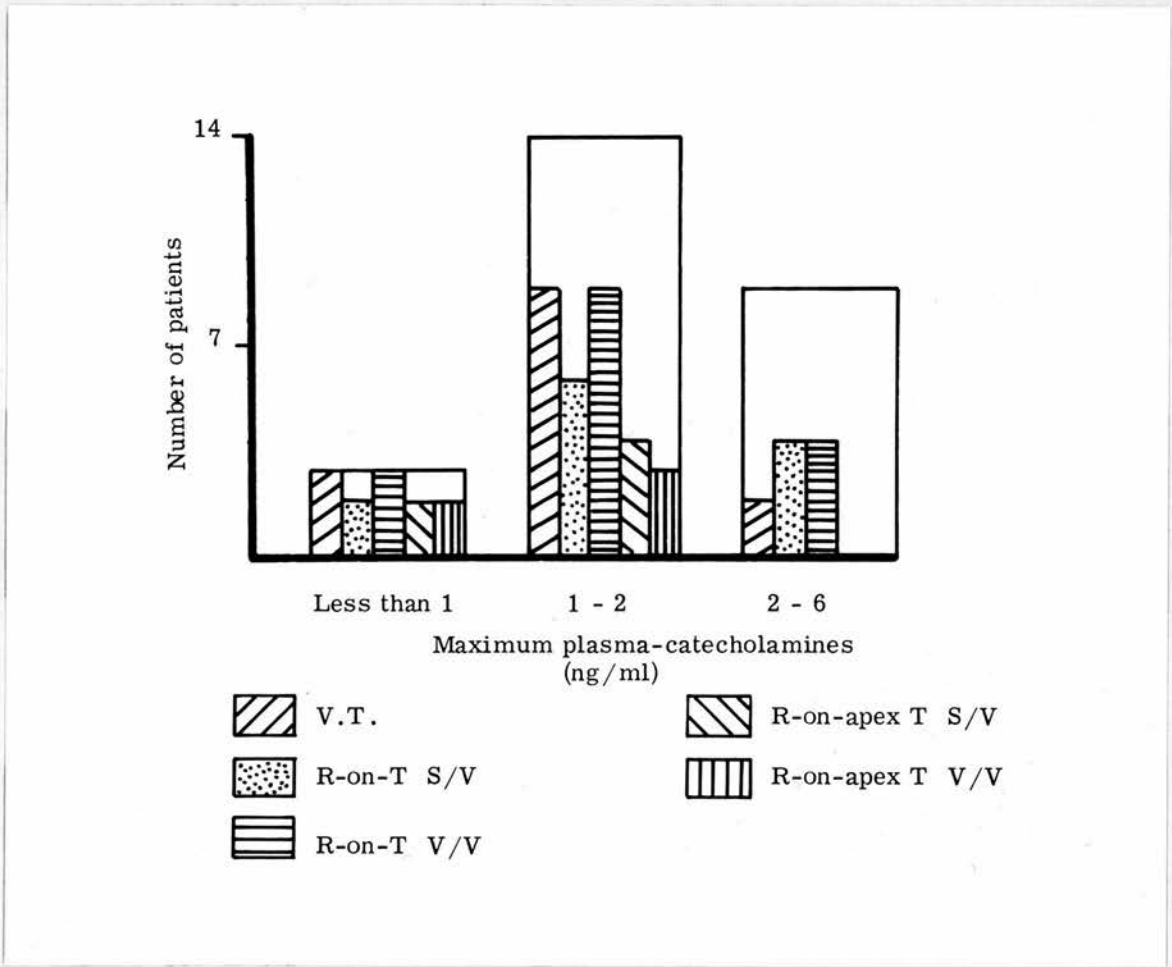

Figure ii. Relationship between Maximum plasma-total-catecholamine concentrations and ventricular arrhythmias.

APPENDIX B

The following publications were produced along with the thesis and include work for the thesis, and work carried out at the same time and in association with the work of the thesis.

1) Rowe, M.J.; Dolder, M.A.; Kirkby, B.J.; Oliver, M.F. (1973) Lancet October 13th pp. 814 - 18 "The Effect of a Nicotinic Acid Analogue on Raised Plasma F.F.A. after Acute Myocardial Infarction."

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4) Strange, R.C.; Vetter, N.J.; Rowe, M.J.; Oliver, M.F., (1974) European Journal of Clinical Investigation 4, 115 - 119 "Plasma cyclic A.M.P. after Acute Myocardial Infarction".

5) Strange, R.C.; Rowe, M.J.; Mjøs, O.D.; Oliver, M.F., (1976) Acta. Med. Scand. 199, 421. "The Effect of Antilipolytic Agents on Cyclic A.M.P., F.F.A. and Total Catecholamine Concentrations in Plasma".

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In the preparation of this thesis I was helped initially by kindly advice from Professor K.W. Donald of the Department of Medicine in the University of Edinburgh and later by criticism of the metabolic elements of the work by Professor O.D. Mjøs of the University of Tromsø in Norway.

I must record most particularly the support given to me by my father-in-law the late Professor D.D. Reid. He encouraged me to embark upon the writing of this thesis, and his sagacious, if sometimes devastating, criticism during its progress largely accounts for the factual reporting of the results and the use of only the simplest of statistical tests.

I greatly enjoyed working along with Dr. R.C. Strange who was responsible for the parallel studies of plasma catecholamines, Dr. A.F. Smith who measured the serum creatine kinase, and Dr. J.M.M. Neilson whose development of the ECG analysis equipment made possible the detailed statements about the individual ventricular arrhythmias.

Mr. W. Adams of the Dept. of Medical Statistics, the Medical/

Medical Illustration and photography services, and the diligent searches for copies of the older references by the librarian and her staff at the Royal College of Physicians of Edinburgh, have all contributed towards the completed work

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